Novel Synthesis of Heterocycles Using Zirconium-Catalyzed Diene Cyclization

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The catalytic cyclization of the diene **1** by Cp_2ZrCl_2 in the presence of BuMgBr gives the hexahydroindole derivative **2**. The stereochemistry of the zirconacycle **10** is different from that of the zirconacycle **7**, which is obtained from **1** under stoichiometric conditions. Carbon–carbon bond formation results from treatment of the intermediary magnesium complex **8** with various electrophiles, such that various heterocycles were synthesized.

Introduction

Zirconium-promoted coupling of nonconjugated dienes, enynes, or diynes constitutes a useful method for the formation of carbon–carbon bonds.[1] In these reactions, a stoichiometric amount of Cp_2ZrBu_2 interacts with two multiple bonds to form a zirconacycle. Since the zirconium–carbon bonds of the zirconacycles are very reactive, they form cyclic compounds with a variety of reagents. Recently, it was reported that carbomagnesiation of alkenes using RMgX in the presence of a titanium or zirconium complex is also an effective method of carbon–carbon bond formation.[2] The cyclomagnesiation of 1,6-heptadienes reported by Waymouth[3] is especially interesting because a zirconacycle is formed from zirconocene, which is generated by RMgX and Cp_2ZrCl_2 and then converts to the dialkylmagnesium complex.

We have previously reported a highly regio- and stereoselective synthesis of nitrogen heterocycles from enynes and dienes, using zirconium-promoted reductive cyclization.[4] These recent reports encouraged us to improve our zirconium-promoted cyclization method. We describe here a new synthesis of heterocycles using RMgX in the presence of a catalytic amount of Cp_2ZrCl_2 and the structure determination of products prepared by zirconium-promoted cyclization or zirconium-catalyzed cyclization.

Scheme 1

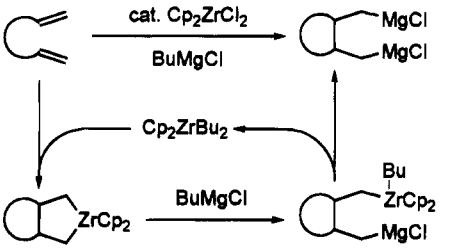

Table 1. Reactions of 1 with BuMgX in the Presence of a Catalytic Amount of Cp_2ZrCl_2[a]

Cp_2ZrCl_2 run (mol %)	X	PPh_3 (mol %)	solvent	temp (°C)	time (h)	yields (%) of 2	3	4	SM
1 (10)	Br		THF	rt	24	32	12	8	32
2 (10)	Br		THF	0	24	6	8	4	79
3 (10)	Br		THF	reflux	4	56	9	31	0
4 (10)	Cl		THF	reflux	3	62	10	28	0
5 (10)	Br		toluene	reflux	1.5	57	9	21	0
6 (10)	Br	20	THF	reflux	2	50	4	18	0
7 (10)	Br	300	THF	reflux	2	45	7	20	0
8 (5)	Br	10	THF	reflux	8	56	6	26	0
9 (2)	Br	4	THF	reflux	25	35	0	35	0

[a] 3 equiv of BuMgX was used in the all reactions.

Zirconium-Catalyzed Diene Cyclization

When a THF solution of the diene **1**, BuMgBr (3 equiv), and a catalytic amount of Cp_2ZrCl_2 (10 mol %) was stirred at room temperature for 24 h, the cyclized products **2** and **3** were obtained in 32% and 12% yields, respectively. The reaction was carried out under various conditions (Table 1). The yield of the desired product **2** was improved to 56% (run 3) when the THF solution was refluxed for 4 h, but the yield was less at lower reaction temperatures. The yield of **2** was slightly improved by the use of BuMgCl instead of BuMgBr (run 4), and toluene is a suitable solvent (run 5). Although a catalytic amount of PPh_3 (20 mol %) accelerated the reaction rate, excess

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(1) (a) Negishi, E.-i.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. (b) Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336. (c) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E.-i. *Tetrahedron Lett.* **1989**, *30*, 5105. (d) Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422. (e) Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435. (f) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7411. (g) Buchwald, S. L.; Lum, R. T.; Dewan, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7441. (h) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047 and references cited in ref 4a.

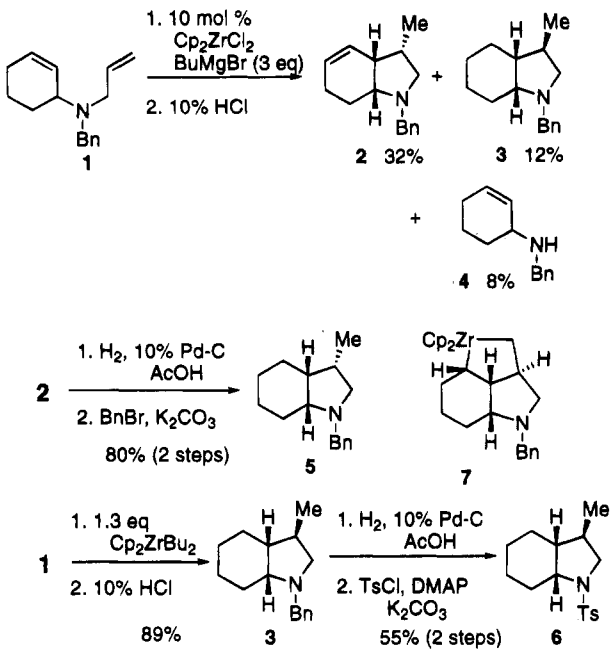
(2) (a) Dzhemilev, U. M.; Vostrikova, O. S. *J. Organomet. Chem.* **1985**, *285*, 43. (b) Dzhemilev, U. M.; Vostrikova, O. S.; Tolstikov, G. A. *J. Organomet. Chem.* **1986**, *304*, 17. (c) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E.-i. *J. Am. Chem. Soc.* **1991**, *113*, 6266. (d) Suzuki, N.; Kondakov, D. Y.; Takahashi, T. *J. Am. Chem. Soc.* **1993**, *115*, 8485. (e) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079. (f) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950. (g) Hoveyda, A. H.; Morken, J. P.; Houri, A. F.; Xu, Z. *J. Am. Chem. Soc.* **1992**, *114*, 6692. (h) Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614. (i) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6997. (j) Hoveyda, A. H.; Morken, J. P. *J. Org. Chem.* **1993**, *58*, 4237. (k) Lewis, D. L.; Muller, P. M.; Whitby, R. J.; Jones, R. V. H. *Tetrahedron Lett.* **1991**, *32*, 6797.

(3) (a) Knight, K. S.; Waymouth, R. M. *J. Am. Chem. Soc.* **1991**, *113*, 6268. (b) Wischmeyer, U.; Knight, K. S.; Waymouth, R. M. *Tetrahedron Lett.* **1992**, *33*, 7735.

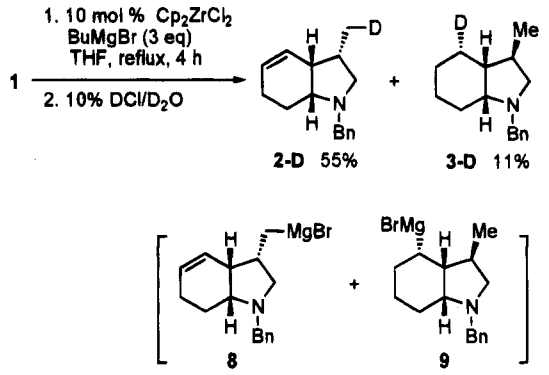
(4) (a) Mori, M.; Uesaka, N.; Shibasaki, M. *J. Org. Chem.* **1992**, *57*, 3519. (b) Mori, M.; Saitoh, F.; Uesaka, N.; Shibasaki, M. *Chem. Lett.* **1993**, 213.

0022-3263/94/1959-4542$04.50/0

Scheme 2



Scheme 3



PPh_3 did not affect the result (runs 6 and 7). Even though a longer reaction time was required, the use of only 5 mol % of Cp_2ZrCl_2 in the presence of 10 mol % of PPh_3 afforded good results (run 8). Less Cp_2ZrCl_2 decreased the amount of cyclized product **3** while the yield of deallylation product **4** increased (run 9).

In order to determine the stereochemistry of the cyclized products, the main product **2** was hydrogenated with 10% palladium on charcoal in AcOH, followed by treatment with benzyl bromide in the presence of K_2CO_3 in CH_3CN, to give **5** in 80% yield. However, the NMR spectrum of compound **5** did not agree with that of compound **3**, which was obtained in 89% yield when diene **1** was treated with a stoichiometric amount of zirconocene,[4a] prepared from Cp_2ZrCl_2 and BuLi (2 equiv).[1a] This means that the stereochemistry of the intermediate zirconacycles in these two reactions is different. However, we could not determine the stereochemistry of compound **3** by NOE experiment,[5] and so studied product **3** by X-ray analysis. Hydrogenation of compound **3** with 10% palladium on charcoal, followed by treatment with tosyl chloride, afforded the tosylamide **6** as a colorless crystal.[6] The X-ray crystallographic analysis structure of compound **6** revealed that the methyl group of compound **6** is *cis* to the ring junction protons. Thus, compound **3** was derived from zirconacycle **7**. The results confirm that the two cyclized products **2** and **3** were derived from the two different zirconacycles.

Possible Reaction Course

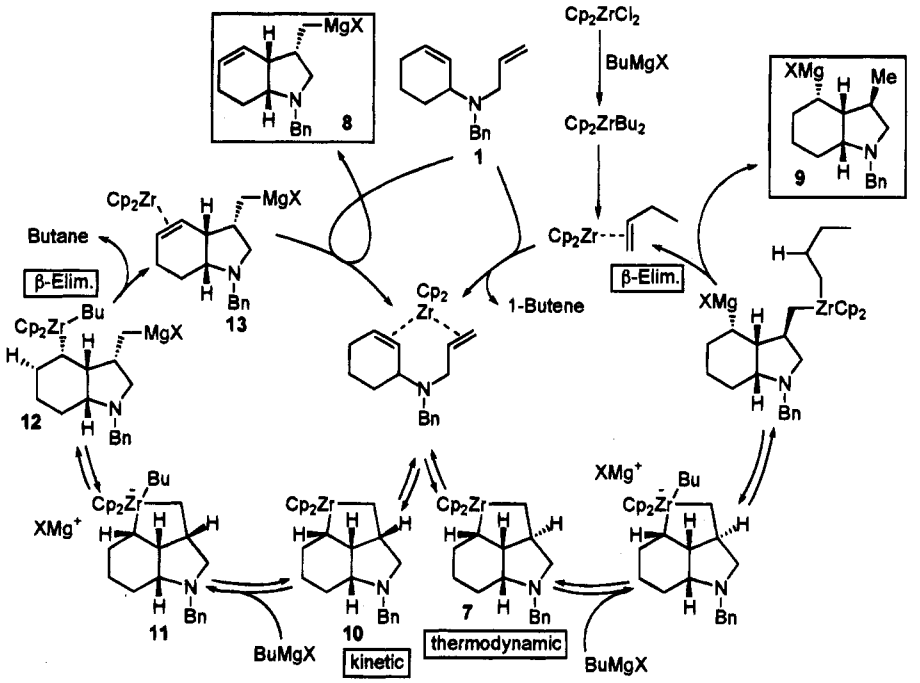
In order to investigate the reaction course, the reaction mixture was quenched with 10% DCl–D_2O to give the deuterated products **2-D** and **3-D** in 55% and 11% yields, respectively. The NMR and mass spectra of these compounds show that deuterium was incorporated at the methyl group of **2-D**, and in **3-D**, deuterium was incorporated at the cyclohexyl moiety. This suggests that the intermediary magnesium complexes in this reaction are **8** and **9**. Given this, the reaction would proceed through zirconacycle **7** or **10** as shown in Scheme 4. Zirconacycle **10** would be produced from the starting diene **1** and zirconocene, which is generated from a catalytic amount of Cp_2ZrCl_2 and BuMgX. Then excess BuMgX would react with **10** to produce the ate complex **11**, whose carbon–zirconium bond fission would occur to give complex **12**. Then, β-hydride elimination would occur to give butane and zirconocene that is coordinated with the cyclohexenyl moiety of **13**. The magnesium complex **8** would be liberated from complex **13**, and the zirconocene would be coordinated with the starting material. Thus, the catalytic cycle would be established. The magnesium complex **9** would be formed from zirconacycle **7**, since zirconacycle **10** is in a state of equilibrium with zirconacycle **7**. The latter zirconacycle **7** would be a thermodynamic product of the reaction of the diene **1** and Cp_2ZrBu_2, derived from Cp_2ZrCl_2 and BuLi or BuMgX.

Our reasoning that zirconacycle **10** is a kinetic product and **7** is a thermodynamic product is based on the following: When a THF solution of the diene **1** and Cp_2ZrBu_2 (1.3 equiv) was stirred at room temperature for 2.5 h, followed by treatment with 10% HCl, the cyclized product **3** was obtained in 89% yield.[4a] The same reaction was carried out at room temperature for 45 min, followed by a similar treatment, to afford the cyclized product **3** in 43% yield along with compounds **2** and **5** (10% and 12% yields, respectively). When the reaction was carried out at 0 °C for 3 h, followed by treatment with 10% HCl, the cyclized product **3** resulted, in 34% yield, along with **2** and **5** (7% and 12% yields, respectively). Evidently, compounds **2** and **5** were derived from zirconacycle **10**. Presumably, the product **2** would be formed by β-hydride elimination from zirconacycle **10**. Since the yields of **2** and **5** decreased when the reaction was carried out at elevated temperature for a longer time, the zirconacycle **10** must be the kinetic product. Why β-hydride elimina-

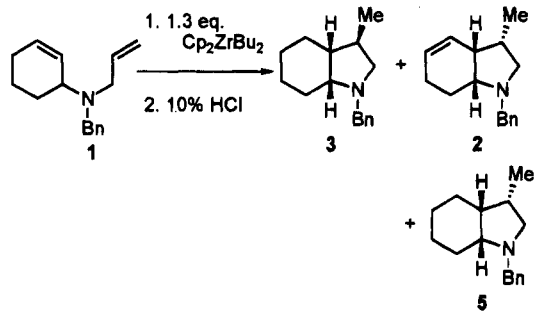
(5) In the previous paper,[4a] we reported the synthesis of heterocycles using zirconium-promoted reductive cyclization and a formal total synthesis of (−)-dendrobine (**23**) using this method. The key compound **27** for the synthesis of (−)-dendrobine (**23**) was prepared by the reaction of the diene **24** with Cp_2ZrBu_2 followed by treatment with carbon monoxide. The stereochemistry of **27** was determined by an NOE experiment on hexahydroindole derivative **26**, which was prepared by the hydrolysis of the zirconacycle **25**. Evidently, the rings of the intermediary zirconacycle for the synthesis of (−)-dendrobine are all *cis*. On the basis of these results, we considered that the stereochemistry of the perhydroindole derivative, prepared by the reaction of the diene **1** with a stoichiometric amount of Cp_2ZrBu_2 followed by hydrolysis, is **5** as shown in Scheme 2. From the results of the X-ray analysis,[6] we must correct the stereochemistry of the perhydroindole derivative as **3**, not **5** (in our previous report,[4a] the stereochemistry of compound **8**). Probably the stereochemistry of the zirconacycle is controlled by the steric or electronic factors in the starting diene. See Scheme 7.

(6) The author has deposited atomic coordinates for this structure with Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 4



Scheme 5



tion occurs from the cyclohexyl moiety of compound **12** instead of the butyl group is not clear[7] and the detailed mechanism is now being investigated. Professor Waymouth had pointed out significant differences in the stereochemistry of the catalytic and the stoichiometric cyclizations of nonconjugated dienes.[3] Namely, 1,7-octadiene cyclizes under kinetically controlled conditions to give *cis* zirconacycle (*cis*:*trans* = 82:18). This result is similar to that seen in stoichiometric reactions.[1c,e] In contrast, the stoichiometric cyclization of 1,6-heptadiene gives the *trans* metalacycles (*cis*:*trans* = 3:97), while catalytic cyclization gives significant *cis* product (*cis*:*trans* = 36:64). Interestingly, the catalytic cyclization of *N*,*N*-diallylaniline is reported to give predominantly *cis* product (*cis*:*trans* = 67:33), while the stoichiometric cyclization of diallyl benzylamine gives *trans* product.[1c] In the present reaction, the stoichiometric cyclization of diene **1** gives the *trans* zirconacycle **7**, while catalytic cyclization of the diene **1** gives predominantly *cis* product **10**.

Conversion of Magnesium Complex into Various Heterocycles

The magnesium complex **8** was a useful intermediate for the synthesis of numerous heterocycles. Treatment of the reaction mixture with iodine afforded the iodinated product **14** in 43% yield. The atmosphere of the vessel containing the reaction mixture was changed from argon to oxygen at −78 °C, and the solution was stirred at that temperature under oxygen for 2 h, followed by treatment with 10% HCl, to give the alcohol **15** in 41% yield. Moreover, new carbon−carbon bonds could be formed using the magnesium complex **8**. Excess benzaldehyde was added to the reaction mixture to provide the condensation product **17** in 29% yield. Compound **17** was converted into **18** by a Jones oxidation. Treatment of **8** with allyl bromide afforded the allylated product **16** in 25% yield. Thus, various heterocycles could be obtained from diene **1** in one-pot reactions.

The diene **16** was treated with dibutylzirconocene (Cp_2ZrBu_2, 1.5 equiv) and then with 10% HCl to provide the

Table 2. Reactions of 1 with Cp_2ZrBu_2 under Various Conditions

			yields (%) of			
run	temp (°C)	time (h)	**3**	**2**	**5**	SM
1	rt	2.5	89			
2	rt	0.75	43	10	12	31
3	0	3	34	7	12	32

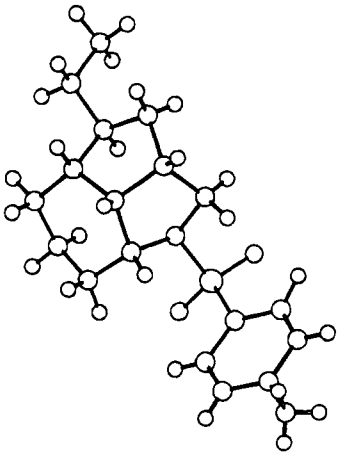
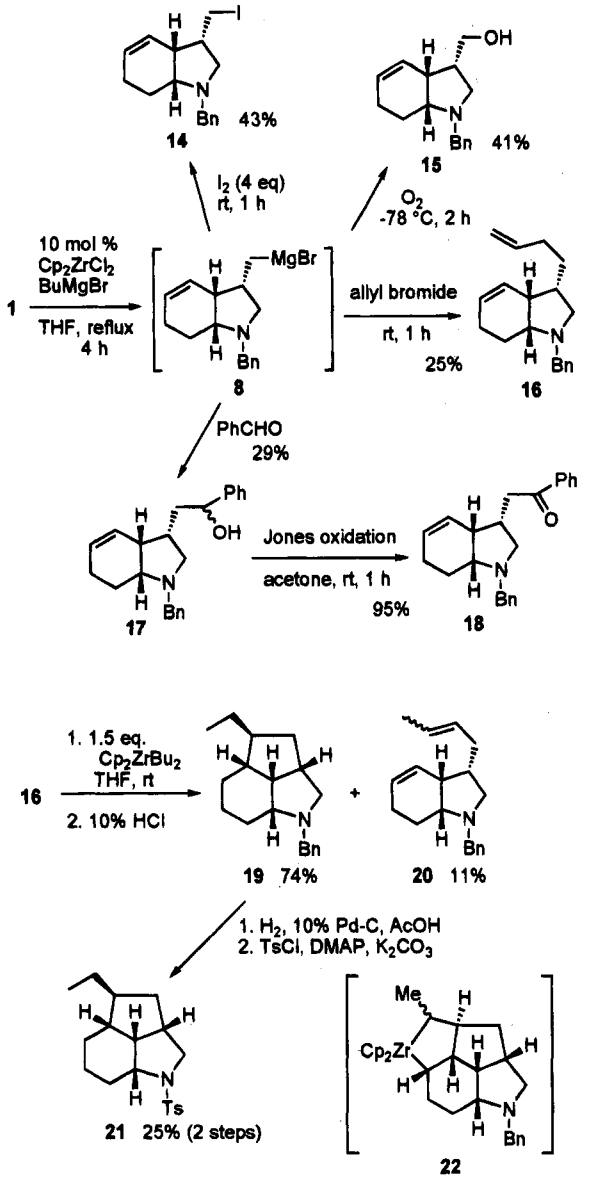


Figure 1. A perspective view of 21.

(7) Negishi, E.-i.; Nguyen, T.; Maye, J. P.; Choueri, D.; Suzuki, N.; Takahashi, T. *Chem. Lett.* **1992**, 2367.

Scheme 6

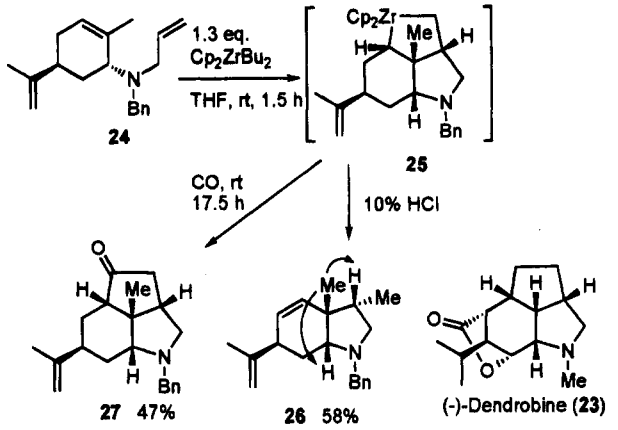


cyclized product **19** in 74% yield along with the olefin isomerization product **20** (11% yield). The stereochemistry of **19** was determined by X-ray analysis of its tosylamide **21**.[6] A perspective view of **21** is shown in Figure 1. The product has a five-membered ring bearing an ethyl group. All the ring junction protons are *cis*, and the ethyl group on the five-membered ring is *cis* to the ring junction protons. Presumably, the five-membered zirconacycle **22** would be formed after the isomerization of the olefin, catalyzed by zirconocene.[8] The X-ray analysis of **21** also suggests that the stereochemistry of the methyl group of compound **2** is *trans* to the ring junction protons.

The most remarkable characteristics of this reaction are as follows: The procedure is very simple and only a catalytic amount of Cp_2ZrCl_2 is required. The stereochemistry of the product obtained under kinetic conditions is different from that of the product obtained under stoichiometric conditions. The intermediary magnesium complex is useful for the synthesis of a variety of heterocycles. Investigations of this system are continuing.

(8) Maye, J. P.; Negishi, E.-i. *Tetrahedron Lett.* **1993**, *34*, 3359.

Scheme 7



Experimental Section

All manipulations were performed under an argon atmosphere. Solvents were distilled under an argon atmosphere from sodium benzophenone (THF) or CaH_2 (CH_2Cl_2). All other reagents and solvents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (70–230 mesh, 60 Å), and flash chromatography was performed on silica gel 60 (230–400 mesh, 60 Å) using the indicated solvent.

(3*S,3a*R**,7a*R**)-1-Benzyl-3-methyl-2,3,3a,6,7,7a-hexahydroindole (2) and (3*R**,3a*R**,7a*R**)-1-Benzyl-3-methylperhydroindole (3).** To a stirred suspension of Cp_2ZrCl_2 (13.8 mg, 0.044 mmol) and **1** (100.3 mg, 0.44 mmol) in THF (1.5 mL) was added dropwise BuMgBr (0.88 M solution in THF, 1.50 mL, 1.32 mmol) at 0 °C. After the solution was stirred at rt for 24 h, to it was added 10% HCl (1.0 mL) at 0 °C, and the mixture was stirred at rt for 1 h. The resultant solution was basified with K_2CO_3 and diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:40, 1:10, 1:0) to afford 31.7 mg (32%) of **2**, 11.7 mg (12%) of **3**, and 6.7 mg (8%) of **4** as colorless oils. **2**: IR (neat) 1650, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.92 (d, J = 7.0 Hz, 3 H), 1.58–1.68 (m, 2 H), 1.76–1.91 (m, 1 H), 2.13–2.39 (m, 2 H), 2.52 (dd, J = 1.9, 6.4 Hz, 1 H), 2.61–2.73 (m, 1 H), 2.92 (ddd, J = 5.7, 5.9, 6.4 Hz, 1 H), 3.43 (d, J = 13.6 Hz, 1 H), 3.94 (d, J = 13.6 Hz, 1 H), 5.57 (dddd, J = 2.0, 2.0, 3.4, 10.0 Hz, 1 H), 5.83 (dddd, J = 1.3, 3.3, 4.6, 10.0 Hz, 1 H), 7.16–7.37 (m, 5 H); MS (EI, *m/z*) 227 (M^+), 212, 91 (bp); HRMS (EI, *m/z*) for $C_{16}H_{21}N$ calcd 227.1674, found 227.1686. Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.63; H, 9.47; N, 6.04. **3**: IR (neat) 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J = 6.8 Hz, 3 H), 1.22–1.35 (m, 2 H), 1.48–1.70 (m, 7 H), 1.76–1.85 (m, 1 H), 1.88 (dd, J = 6.4, 8.8 Hz, 1 H), 2.66 (ddd, J = 4.9, 4.9, 4.9 Hz, 1 H), 3.11 (dd, J = 8.1, 8.8 Hz, 1 H), 3.27 (d, J = 13.2 Hz, 1 H), 3.91 (d, J = 13.2 Hz, 1 H), 7.18–7.39 (m, 5 H); MS (EI, *m/z*) 229 (M^+), 186, 91 (bp); HRMS (EI, *m/z*) for $C_{16}H_{23}N$ calcd 229.1831, found 229.1828. Anal. Calcd for its picrate $C_{22}H_{26}N_4O_7$: C, 57.64; H, 5.72; N, 12.22. Found: C, 57.54; H, 5.81; N, 12.10. Mp of picrate 133.5–135.0 °C (recrystallized from Et_2O).

(3*S,3a*R**,7a*R**)-1-Benzyl-3-(deuteriomethyl)-2,3,3a,6,7,7a-hexahydroindole (2-D) and (3*R**,3a*R**,4*S**,7a*R*)-1-Benzyl-4-deuterio-3-methylperhydroindole (3-D).** To a stirred suspension of Cp_2ZrCl_2 (6.5 mg, 0.022 mmol) and **1** (50.3 mg, 0.22 mmol) in THF (0.75 mL) was added dropwise BuMgBr (0.85 M solution in THF, 0.78 mL, 0.66 mmol) at 0 °C. After the solution was refluxed with stirring for 3.5 h, to it was added 10% HCl (1.0 mL) at 0 °C, and the mixture was stirred at rt for 1 h. The resultant solution was basified with K_2CO_3 and diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:40, 1:10, 1:0) to afford 27.8 mg (55%) of **2-D**, 5.7 mg (11%) of **3-D**, and 7.0 mg (17%) of **4** as colorless oils.

2-D: IR (neat) 1650, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (br.d, J = 7.0 Hz, 2 H), 1.58–1.68 (m, 2 H), 1.76–1.91 (m, 1 H), 2.13–2.39 (m, 2 H), 2.52 (dd, J = 1.9, 6.4 Hz, 1 H), 2.61–2.73 (m, 1 H), 2.92 (ddd, J = 5.7, 5.9, 6.4 Hz, 1 H), 3.43 (d, J = 13.6 Hz, 1 H), 3.94 (d, J = 13.6 Hz, 1 H), 5.57 (dddd, J = 2.0, 2.0, 3.4, 10.0 Hz, 1 H), 5.83 (dddd, J = 1.3, 3.3, 4.6, 10.0 Hz, 1 H), 7.16–7.37 (m, 5 H); MS (EI, m/z) 228 (M^+), 212, 137, 91 (bp); HRMS (EI, m/z) for $C_{16}DH_{20}N$ calcd 228.1736, found 228.1741. **3-D**: IR (neat) 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.94 (d, J = 6.8 Hz, 3 H), 1.22–1.35 (m, 2 H), 1.48–1.70 (m, 6 H), 1.76–1.85 (m, 1 H), 1.88 (dd, J = 6.4, 8.8 Hz, 1 H), 2.66 (ddd, J = 4.9, 4.9, 4.9 Hz, 1 H), 3.11 (dd, J = 8.1, 8.8 Hz, 1 H), 3.27 (d, J = 13.2 Hz, 1 H), 3.91 (d, J = 13.2 Hz, 1 H), 7.18–7.39 (m, 5 H); MS (EI, m/z) 230 (M^+), 215, 187, 91 (bp); HRMS (EI, m/z) for $C_{16}DH_{22}N$ calcd 230.1893, found 230.1889.

(3S*,3aR*,7aR*)-1-Benzyl-3-methylperhydroindole (5). A suspension of **2** (35.7 mg, 0.16 mmol) and 10% Pd on charcoal (36.2 mg) in AcOH (3.0 mL) was stirred at rt for 5 h. After the catalyst was filtered off, the solvent was removed. To the residue in CH_2Cl_2 (3.0 mL) containing K_2CO_3 (221.0 mg, 1.6 mmol) was added benzyl bromide (0.095 mL, 0.8 mmol) at 0 °C. After the suspension was stirred at rt for 7 h, to it was added H_2O (1.0 mL) at 0 °C, and the resultant mixture was diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:8) to afford 29.4 mg (80%) of **5** as a colorless oil: IR (neat) 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.84 (d, J = 7.0 Hz, 3 H), 1.08–1.92 (m, 9 H), 2.10–2.29 (m, 1 H), 2.45 (dd, J = 9.7, 9.7 Hz, 1 H), 2.64 (dd, J = 9.0, 9.0 Hz, 1 H), 2.75–2.84 (m, 1 H), 3.23 (d, J = 14.7 Hz, 1 H), 3.99 (d, J = 14.7 Hz, 1 H), 7.15–7.41 (m, 5 H); MS (EI, m/z) 229 (M^+), 214, 91 (bp); HRMS (EI, m/z) for $C_{16}H_{23}N$ calcd 229.1830, found 229.1829. Anal. Calcd for $C_{16}H_{23}N$: C, 83.79; H, 10.11; N, 6.11. Found: C, 83.66; H, 10.25; N, 5.71.

(3R*,3aR*,7aR*)-3-Methyl-1-tosylperhydroindole (6). A suspension of **3** (14.2 mg, 0.062 mmol) and 10% Pd on charcoal (14.4 mg) in AcOH (0.5 mL) was stirred at rt for 3 h. After the catalyst was filtered off, the solvent was removed. To the residue in CH_2Cl_2 (0.5 mL) containing K_2CO_3 (171.9 mg, 1.24 mmol) and DMAP (1.7 mg, 0.014 mmol) was added tosyl chloride (118.3 mg, 0.62 mmol) at 0 °C. After the suspension was stirred at rt for 21 h, to it was added H_2O (1.0 mL) at 0 °C, and the resultant mixture was diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:15) to afford 10.0 mg (55%) of **6** as a colorless crystal: mp 118.0–119.0 °C (recrystallized from Et_2O); IR (KBr) 1600, 1335, 1155 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 3 H), 1.08–1.73 (m, 8 H), 1.92–2.06 (m, 1 H), 2.11–2.30 (m, 1 H), 2.43 (s, 3 H), 2.69 (dd, J = 9.4, 9.4 Hz, 1 H), 3.61 (dd, J = 7.5, 9.4 Hz, 1 H), 3.66 (ddd, J = 6.3, 6.3, 10.3 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.72 (d, J = 8.2 Hz, 2 H); MS (EI, m/z) 293 (M^+), 278, 250 (bp), 155, 138, 91; HRMS (EI, m/z) for $C_{16}H_{23}NO_2S$ calcd 293.1450, found 293.1465. Anal. Calcd for $C_{16}H_{23}NO_2S$: C, 65.49; H, 7.90; N, 4.77; S, 10.93. Found: C, 65.72; H, 7.91; N, 4.80; S, 11.06.

(3S*,3aR*,7aR*)-1-Benzyl-3-(indomethyl)-2,3,3a,6,7,7a-hexahydroindole (14). To a stirred suspension of Cp_2ZrCl_2 (6.6 mg, 0.022 mmol) and **1** (49.6 mg, 0.22 mmol) in THF (0.75 mL) was added dropwise BuMgBr (0.85 M solution in THF, 0.78 mL, 0.66 mmol) at 0 °C. After the mixture was refluxed with stirring for 4.5 h, a solution of I_2 (223.0 mg, 0.88 mmol) in THF (4.0 mL) was added at 0 °C, and the solution was stirred at rt for 1 h. To the solution was added 20% $Na_2S_2O_3$ (1.0 mL) at 0 °C, and the resultant mixture was basified with K_2CO_3 and diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:40, 1:5, 1:0) to afford 33.2 mg (43%) of **14**, 6.5 mg (13%) of **2**, and 6.5 mg (16%) of **4** as colorless oils: IR (neat) 1650, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.52–1.70 (m, 2 H), 1.75–1.92 (m, 1 H), 2.08–2.27 (m, 1 H), 2.57 (dd, J = 7.2, 9.1 Hz, 1 H), 2.59–2.78 (m, 1 H), 2.78 (dd, J = 5.0, 9.1 Hz, 1 H), 2.78–2.89 (m, 1 H), 2.90–3.03 (m, 1 H), 3.15 (dd, J = 7.8, 9.6 Hz, 1 H), 3.20 (dd, J = 6.5, 9.6 Hz, 1 H), 3.44 (d, J = 13.7 Hz, 1 H), 3.94 (d, J = 13.7 Hz, 1 H), 5.58 (br d, J = 9.8 Hz, 1 H), 5.81–5.96 (m, 1 H), 7.08–7.38 (m, 5 H); MS (EI, m/z) 353 (M^+), 226, 212, 91 (bp); HRMS (EI, m/z) for $C_{16}H_{20}IN$ calcd 353.0641, found 353.0633.

(3S*,3aR*,7aR*)-1-Benzyl-3-(hydroxymethyl)-2,3,3a,6,7,-7a-hexahydroindole (15). To a stirred suspension of Cp_2ZrCl_2 (6.4 mg, 0.022 mmol) and **1** (49.9 mg, 0.22 mmol) was added dropwise BuMgBr (0.85 M solution in THF, 0.78 mL, 0.66 mmol) at 0 °C. The solution was refluxed with stirring for 4.5 h, the atmosphere of the vessel was changed from argon to oxygen at −78 °C, and the solution was stirred at −78 °C for 2 h. To the solution was added H_2O (1.0 mL), and the resultant mixture was diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:10, 1:5, 2:1, 1:0) to afford 6.2 mg (12%) of **2** and 22.1 mg (41%) of **15** as colorless oils: IR (neat) 3350, 1650, 1600 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.66–1.78 (m, 2 H), 1.83–1.93 (m, 1 H), 2.12–2.21 (m, 1 H), 2.32–2.40 (m, 1 H), 2.43 (dd, J = 7.0, 9.3 Hz, 1 H), 2.79 (ddd, J = 5.4, 5.4, 8.3 Hz, 1 H), 2.86 (dd, J = 2.5, 9.3 Hz, 1 H), 2.84–2.95 (m, 1 H), 3.30 (d, J = 13.2 Hz, 1 H), 3.59 (dd, J = 4.5, 10.4 Hz, 1 H), 3.63 (dd, J = 5.0, 10.4 Hz, 1 H), 4.03 (d, J = 13.2 Hz, 1 H), 5.67–5.76 (m, 1 H), 5.87–5.96 (m, 1 H), 7.19–7.35 (m, 5 H); MS (EI, m/z) 243 (M^+), 212, 91 (bp); HRMS (EI, m/z) for $C_{16}H_{21}NO$ calcd 243.1623, found 243.1626. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.01; H, 8.86; N, 5.54.

(3S*,3aR*,7aR*)-1-Benzyl-3-(3-butenyl)-2,3,3a,6,7,7a-hexahydroindole (16). To a stirred suspension of Cp_2ZrCl_2 (108.0 mg, 0.37 mmol) and **1** (847.2 mg, 3.73 mmol) in THF (15.0 mL) was added dropwise BuMgBr (0.85 M solution in THF, 13.0 mL, 11.2 mmol) at 0 °C. After the solution was refluxed with stirring for 6.5 h, to it was added allyl bromide (1.6 mL, 18.7 mmol) at 0 °C, and the solution was stirred at rt for 10 h. To the solution was added H_2O (2.0 mL), and the resultant mixture was diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:100, 1:50, 1:10) to afford 225.0 mg (27%) of **1**, 246.5 mg (25%) of **16**, and 265.1 mg (31%) of **2** as colorless oils: IR (neat) 1640, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.19–2.08 (m, 5 H), 2.08–2.35 (m, 2 H), 2.51 (dd, J = 7.9, 9.6 Hz, 1 H), 2.61 (dd, J = 7.7, 9.6 Hz, 1 H), 2.64–2.75 (m, 1 H), 2.91 (ddd, J = 3.0, 5.3, 5.3 Hz, 1 H), 3.47 (d, J = 14.7 Hz, 1 H), 3.95 (d, J = 14.7 Hz, 1 H), 4.92 (dddd, J = 1.1, 1.1, 2.2, 10.2 Hz, 1 H), 4.97 (dddd, J = 1.1, 1.1, 1.9, 17.3 Hz, 1 H), 5.51–5.62 (m, 1 H), 5.76–5.86 (m, 1 H), 5.78 (dddd, J = 6.6, 6.6, 10.2, 17.3 Hz, 1 H), 7.18–7.44 (m, 5 H); MS (EI, m/z) 267 (M^+), 224, 212, 176, 91 (bp); HRMS (EI, m/z) for $C_{19}H_{25}N$ calcd 267.1987, found 267.1968. Anal. Calcd for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.24. Found: C, 85.48; H, 9.46; N, 5.18.

(3S*,3aR*,7aR*)-1-Benzyl-3-(2-hydroxy-2-phenylethyl)-2,3,3a,6,7,7a-hexahydroindole (17). To a stirred suspension of Cp_2ZrCl_2 (6.4 mg, 0.022 mmol) and **1** (49.8 mg, 0.22 mmol) in THF (0.75 mL) was added dropwise BuMgBr (0.85 M solution in THF, 0.78 mL, 0.66 mmol) at 0 °C. After the mixture was refluxed with stirring for 6 h, benzaldehyde (0.09 mL, 0.88 mmol) was added at 0 °C, and the solution was stirred at 0 °C for 1 h. To the solution was added 10% HCl (1.0 mL) at 0 °C, and the resultant mixture was basified with K_2CO_3 and diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:50, 1:1, 1:0) to afford 7.0 mg (14%) of **2**, 20.5 mg (28%, mixture of diastereomers) of **17**, and 7.2 mg (9%) of **4** as colorless oils: IR (neat) 3370, 1650, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.51–2.59 (m, 8 H), 2.53 (dd, J = 7.5, 9.1 Hz, 0.5 H), 2.55 (dd, J = 7.8, 9.6 Hz, 0.5 H), 2.61–2.84 (m, 1 H), 2.73 (dd, J = 5.1, 9.6 Hz, 0.5 H), 2.75 (dd, J = 7.0, 9.1 Hz, 0.5 H), 2.86–3.01 (m, 1 H), 3.48 (d, J = 13.8 Hz, 0.5 H), 3.49 (d, J = 13.4 Hz, 0.5 H), 3.92 (d, J = 13.8 Hz, 0.5 H), 3.94 (d, J = 13.4 Hz, 0.5 H), 4.55–4.70 (m, 1 H), 5.50–5.59 (m, 0.5 H), 5.59–5.72 (m, 0.5 H), 5.77–5.88 (m, 1 H),

7.15–7.50 (m, 10 H); MS (EI, *m/z*) 333 (M^+), 256, 242, 212, 105, 91 (bp); HRMS (EI, *m/z*) for $C_{23}H_{27}NO$, calcd 333.2092, found 333.2084. Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.99; H, 8.39; N, 3.87.

(3*S,3a*R**,7a*R**)-3-(Benzoylmethyl)-1-benzyl-2,3,3a,6,7,-7a-hexahydroindole (18).** To a stirred solution of **17** (4.4 mg, 0.013 mmol) in acetone (0.5 mL) was added Jones reagent (8 N, 0.75 μL) at 0 °C. After the mixture was stirred at rt for 1 h, ^{i}PrOH (1.0 mL) and H_2O (1.0 mL) were added and the resultant mixture was basified with K_2CO_3 and diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:10) to afford 4.3 mg (95%) of **18** as a colorless oil: IR (neat) 1680, 1640, 1590 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.58–1.73 (m, 2 H), 1.77–1.94 (m, 1 H), 2.11–2.29 (m, 1 H), 2.61 (dd, *J* = 6.6, 9.6 Hz, 1 H), 2.65 (dd, *J* = 4.3, 9.6 Hz, 1 H), 2.81–3.01 (m, 4 H), 3.12 (dd, *J* = 5.1, 16.9 Hz, 1 H), 3.43 (d, *J* = 13.4 Hz, 1 H), 3.97 (d, *J* = 13.4 Hz, 1 H), 5.44–5.58 (m, 1 H), 5.78–5.91 (m, 1 H), 7.16–7.58 (m, 8 H), 7.89–7.96 (m, 2 H); MS (EI, *m/z*) 331 (M^+), 254, 211, 120, 105, 91 (bp); HRMS (EI, *m/z*) for $C_{23}H_{25}NO$ calcd 331.1936, found 331.1947. Anal. Calcd for $C_{23}H_{25}NO$: C, 83.35; H, 7.60; N, 4.23. Found, C, 83.24; H, 7.79; N, 4.28.

(1*S,3*S**,4*R**,8*R**,11*R**)-9-Benzyl-3-ethyl-9-azatricyclo-[6.2.1.0^{4,11}]undecane (19) and (3*S**,3a*R**,7a*R**)-1-Benzyl-3-(2-butenyl)-2,3,3a,6,7,7a-hexahydroindole (20).** To a stirred suspension of Cp_2ZrCl_2 (49.2 mg, 0.17 mmol) in THF (0.5 mL) was added dropwise BuLi (1.63 M solution in hexane, 0.20 mL, 0.32 mmol) at −78 °C. After the mixture was stirred at −78 °C for 1 h, a solution of **16** (30.3 mg, 0.11 mmol) in THF (1.0 mL) was added. The reaction mixture was allowed to warm to rt and stirred for 5 h. To the solution was added 10% HCl (1.0 mL) at 0 °C, and the resultant mixture was stirred at rt for 1 h, basified with K_2CO_3, and diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:50, 1:10) to afford 22.0 mg (74%) of **19** and 3.4 mg (11%) of **20** as colorless oils. **19**: IR (neat) 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.88 (t, *J* = 6.7 Hz, 3 H), 1.10–1.28 (m, 2 H), 1.32–1.84 (m, 6 H), 1.88–2.10 (m, 2 H), 2.11 (dd, *J* = 9.2, 9.2 Hz, 1 H), 2.22–2.52 (m, 2 H), 2.63 (d, *J* = 9.2 Hz, 1 H), 2.73 (d, *J* = 13.5 Hz, 1 H), 4.00 (d, *J* = 13.5 Hz, 1 H), 7.14–7.38 (m, 5 H); MS (EI, *m/z*) 269 (M^+), 178, 91 (bp); HRMS (EI, *m/z*) for $C_{19}H_{27}N$, calcd 269.2144, found 269.2166. Anal. Calcd for $C_{19}H_{27}N$: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.49; H, 10.23; N, 5.02. **20**: IR (neat) 1640, 1600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.05–2.36 (m, 7 H), 2.45 (dd, *J* = 8.0, 9.5 Hz, 1 H), 2.63 (dd, *J* = 6.9, 9.5 Hz, 1 H), 2.65–2.83 (m, 1 H), 2.88–3.02 (m, 1 H), 1.61 (s, 3 H), 3.45 (d, *J* = 13.8 Hz, 1 H), 3.95 (d, *J* = 13.8 Hz, 1 H), 5.25–5.48 (m, 2 H), 5.51–5.65 (m, 1 H), 5.75–5.87 (m, 1 H), 7.15–7.46 (m, 5 H); MS (EI, *m/z*) 267 (M^+), 212, 120, 91 (bp); HRMS (EI, *m/z*) for $C_{19}H_{25}N$ calcd 267.1987, found 267.2007.

(1*S,3*S**,4*R**,8*R**,11*R**)-3-Ethyl-9-tosyl-9-azatricyclo-[6.2.1.0^{4,11}]undecane (21).** A suspension of **19** (109.1 mg, 0.40 mmol) and 10% Pd on charcoal (100.0 mg) in AcOH (4.0 mL) was stirred at rt for 3 h. After the catalyst was filtered off, the solvent was removed. To the residue in CH_2Cl_2 (4.0 mL) containing K_2CO_3 (1.10 g, 8.0 mmol) and DMAP (9.0 mg, 0.074 mmol) was added tosyl chloride (762.5 mg, 4.0 mmol) at 0 °C. After the suspension was stirred at rt for 19 h, to it was added H_2O (1.0 mL) at 0 °C, and the resultant mixture was diluted with AcOEt. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (AcOEt–hexane, 1:10) to afford 33.4 mg (25%) of **21** as colorless crystals: mp 117.5–118.5 °C (recrystallized from acetone); IR (KBr) 1340, 1160 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, *J* = 6.0 Hz, 3 H), 1.15–1.99 (m, 10 H), 2.25–2.51 (m, 1 H), 2.43 (s, 3 H), 2.53–2.68 (m, 1 H), 2.72 (ddd, *J* = 3.2, 3.2, 6.8 Hz, 1 H), 2.92 (dd, *J* = 8.7, 10.0 Hz, 1 H), 3.32 (dd, *J* = 2.2, 10.0 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 7.63 (d, *J* = 8.2 Hz, 2 H); MS (EI, *m/z*) 333 (M^+), 178 (bp), 91; HRMS (EI, *m/z*) for $C_{19}H_{27}NO_2S$ calcd 333.1762, found 333.1743. Anal. Calcd for $C_{19}H_{27}NO_2S$: C, 68.43; H, 8.16; N, 4.20. Found: C, 68.24; H, 8.29; N, 4.22.