Palladium(II)-Catalyzed 1,4-Oxidation of 2-Aryl-1,3-cyclohexadienes. Application to the Synthesis of (±)-Epibatidine and Analogues

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Palladium(II)-catalyzed 1,4-chloroacetoxylation of 2-aryl-1,3-cyclohexadienes **2a** and **2b** resulted in a highly regio- and stereoselective reaction to give *cis*-1-acetoxy-3-aryl-4-chloro-2-cyclohexenes **7a** and **7b**, respectively. The phenyl adduct **7a** was subjected to the synthesis of *exo*- and *endo*-2-phenyl-7-azabicyclo[2.2.1]heptanes (*exo*-**1a** and *endo*-**1a)**. Stereoselective allylic nucleophilic substitution of the chloro group in **7a** by tosylamide with either retention or inversion and hydrolysis to give **9a** and **14a**, respectively, followed by hydrogenation, cyclization, and deprotection afforded the target molecules. Interestingly, stereoselective hydrogenation of intermediates **9a** and **14a** afforded the required 1,2-*cis* and 1,2-*trans* relationships, respectively, between the nitrogen and the phenyl group. In an analogous manner, **7b** was transformed to *exo*-**12b**, which previously has been converted to epibatidine.

Introduction

Regio- and stereoselective 1,4-functionalization of conjugated dienes via palladium(II)-catalyzed 1,4-diacyloxylation and 1,4-haloacyloxylation has developed into useful synthetic methodology.[1−4] In particular, 1,4-functionalization via palladium(II)-catalyzed 1,4-chloroacetoxylation has been frequently employed in regio- and stereoselective organic synthesis. The chloroacetoxylation of conjugated dienes proceeds with high 1,4-syn selectivity and, for substituted dienes, good diastereo- and regioselectivity are often obtained. For example, cyclic 2-substituted dienes give exclusively 1-acetoxy 4-chloro 3-substituted 2-alkenes.[2a,3b] However, there are no examples where 2-aryl substituted 1,3-dienes are employed. We have previously reported on the transformation of 1,3-cycloheptadienes to *cis*- and *trans*-4-amido-2-cycloheptenol derivatives and subsequent cyclization to tropane alkaloids.[3c,d] The corresponding sequence applied to 1,3-cyclohexadienes would afford 7-azabicyclo[2.2.1]heptane systems (**1**) according to Scheme 1.

Recently there has been a great interest in aryl-substituted 7-azabicyclo[2.2.1]heptanes, mainly due to the discovery of the alkaloid epibatidine (**1b**) which was isolated and characterized in 1992 by Daly[5] et al. Epibatidine has been shown to possess remarkable analgesic properties (>200 times as active as morphine), and its synthesis has attracted considerable attention.[6,7] It was therefore of interest to study the palladium(II)-catalyzed 1,4-oxidation of 2-aryl-1,3-cyclohexadienes. In this paper we report on regio- and stereoselective 1,4-functionalization of 2-aryl-1,3-cyclohexadienes (**2**) via palladium(II)-catalyzed 1,4-chloroacetoxylation, and the application to the synthesis of bicyclic systems **1**.

Results and Discussion

Preparation of Starting Materials. Synthesis of the 2-phenyl-1,3-cyclohexadiene **2a** was carried out according

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(1) (a) Bäckvall, J. E. Palladium-Catalyzed 1,4-Additions to Conjugated Dienes. Review in *Metal-catalyzed Cross Coupling Reactions*; Stang, P., Diederich, F., Eds.; VCH: Weinham, 1998; pp 339−382. (b) Bäckvall, J. E. In *The Chemistry of Functional Groups: Polyenes and Dienes*; Patai S., Rappoport, Z., Eds.; Wiley: New York, 1996; pp 653−682. (c) Harrington, P. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12 (Vol. Ed. Hegedus, L. S.), p 797. (d) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, 1995.

(2) (a) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676. (b) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem*. **1984**, *49*, 4619.

(3) (a) Andersson, P. G.; Bäckvall, J. E. In *Advances in Natural Product Synthesis*; Pearson, W., Ed.; JAI Press: Greenwich, CT, 1996; pp 179−215. (b) Tanner, D.; Sellén, M.; Bäckvall, J. E. *J. Org. Chem*. **1989**, *54*, 3374. (c) Schink H. E.; Pettersson, H.; Bäckvall, J. E. *J. Org. Chem*. **1991**, *56*, 2769. (d) Bäckvall, J. E.; Renko, Z. D.; Byström, S. E. *Tetrahedron Lett*. **1987**, *28*, 4199.

(4) Some selected examples where this methodology has been used by others in natural product synthesis, see: (a) Pearson, A. J.; Lai, Y. S.; Lu, W.; Pinkerton, A. A. *J. Org. Chem*. **1989**, *54*, 3882. (b) Oppolzer, W.; DeVita, R. J. *J. Org. Chem*. **1991**, *56*, 6256. (c) Johnson, C. R.; Golebiowski, A.; Steensma, D. H.; Scialdone, M. A. *J. Org. Chem*. **1993**, *58*, 7185. (d) Johnson, C. R.; Bis, S. J. *J. Org. Chem*. **1995**, *60*, 615.

(5) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.

(6) Broka, C. *Med. Chem. Res.* **1994**, *4*, 449; this review describes nine total syntheses until September 1994. For later work not covered by this review, see ref 7 and (b) Ko, S. Y.; Lerpiniere, J.; Linney, I. D.; Wrigglesworth, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1775. (c) Senokuchi, K.; Nakai, H.; Kawamura, M.; Katsube, N.; Nonaka, S.; Sawaragi, H.; Hamanaka, N. *Synlett* **1994**, 343. (d) Aben, R. W. M.; Keijsers, J.; Hams, B.; Kruse, C. G.; Scheeren, H. W. *Tetrahedron Lett*. **1994**, *35*, 1299. (e) Pandey, G.; Bagul, T. D.; Lakshmaiah, G. *Tetrahedron Lett*. **1994**, *35*, 7439. (f) Albertini, E.; Barco, A.; Beretti, S.; De Risi, C.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, *35*, 9297. (g) Kotian, P. L.; Carroll, F. I. *Synth. Commun.* **1995**, *25*, 63. (h) Gonzales, J.; Koontz, J. I.; Hodges, L. M.; Nilsson, K. R.; Neely, L. K.; Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1995**, *117*, 3405. (i) Hernández, A.; Marcos, M.; Rapoport, H. *J. Org. Chem*. **1995**, *60*, 2683. (j) Chen, Z.; Trudell, M. L. *Chem. Rev*. **1996**, *96*, 1179.

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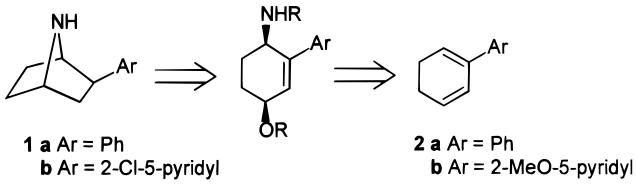
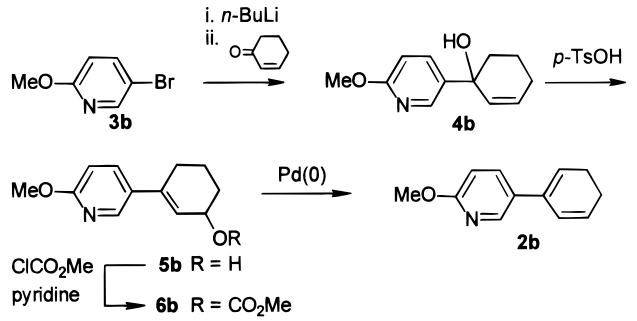
Scheme 1



Scheme 2

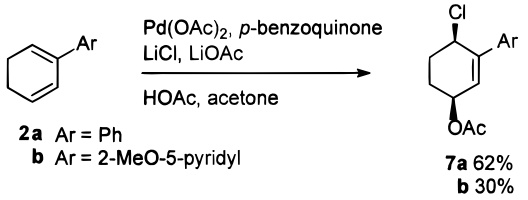


to a known procedure developed in this laboratory.[8] The synthesis of **2b** is shown in Scheme 2 and starts from 5-bromo-3-methoxypyridine (**3**) and 2-cyclohexen-1-one. Lithiation of **3** followed by 1,2-addition to 2-cyclohexen-1-one afforded allylic alcohol **4**. Treatment of **4** with *p*-toluenesulfonic acid resulted in the rearranged allylic alcohol **5**. Reaction of **5** with methyl chloroformate gave the corresponding allylic carbonate (**6b**) which upon treatment with $Pd(PPh_3)_4$ resulted in a regioselective elimination to give diene **2b**.

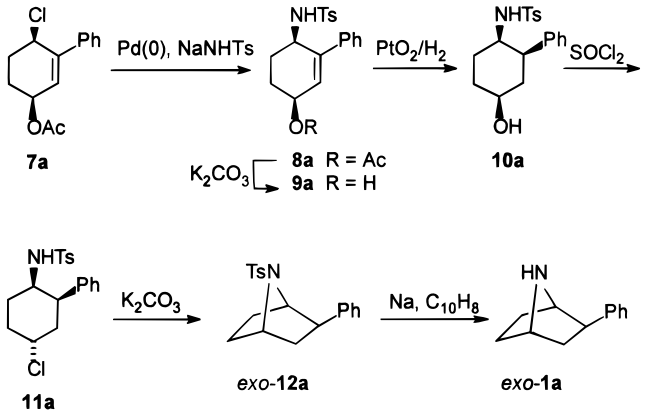
Stereoselective Synthesis of Bicycles *exo*- and *endo*-1. A. 1,4-Chloroacetoxylation. Palladium(II)-catalyzed chloroacetoxylation of 2-phenyl-1,3-cyclohexadiene (**2a**) employing $Pd(OAc)_2$, *p*-benzoquinone, LiCl, and LiOAc in acetone−acetic acid[3b,9] afforded chloroacetate **7a** in 62% yield in a highly regio- and stereoselective reaction. The corresponding chloroacetoxylation of the methoxypyridyl diene **2b** was less efficient and gave the corresponding adduct **7b** in only 30% yield (Scheme 3).

B. Synthesis of *exo*-1a. To reach the *exo*-analogue (**1a**) the *cis*-chloroacetate **7a** was transformed into the *cis*-amidoacetate **8a** by $Pd(PPh_3)_4$-catalyzed allylic substitution with NaNHTs in acetonitrile, in 79% yield (Scheme 4). Acetate **8a** was hydrolyzed, and the resulting allylic alcohol **9a** was subsequently hydrogenated employing 7% of Adam's catalyst in ethanol. The hydrogenation proceeded with high stereoselectivity, and **10a** was isolated in 94% yield, as a single diastereomer. In this way the *cis* stereochemistry, between the phenyl and the tosylamido groups, required for the *exo* compound, was created. The *trans* 1,4-relationship required for the cyclization was achieved by inversion of the stereochemistry at C-1. Replacement of the hydroxyl group with chloride, using thionyl chloride, gave **11a** in 66% yield. Cyclization in methanol employing K_2CO_3 as base gave the *N*-tosyl-protected compound, *exo*-**12a**, in 95% yield. Detosylation of **12a** by sodium naphthhalenide[10] afforded the target molecule, *exo*-**1a** in 97% yield.

Scheme 3

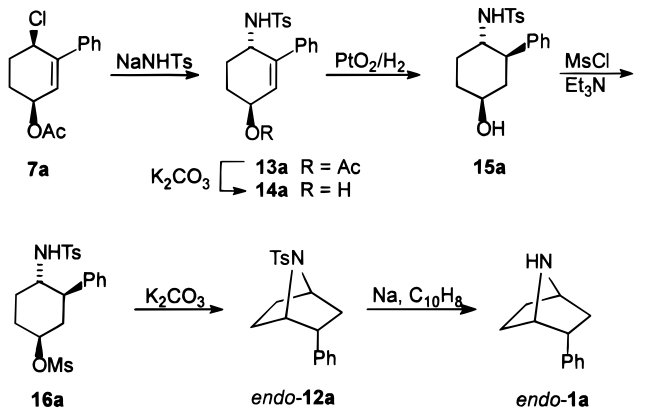


Scheme 4



C. Synthesis of *endo*-1a. For the synthesis of compound *endo*-**12a** a *trans* relationship between the nitrogen and the phenyl group is required. Hydrogenation of allylic alcohol **9a** from the β-face would produce *epi*-**10a** with phenyl *trans* to nitrogen. It is known that a hydroxy group can direct a metal-catalyzed hydrogenation to the *syn*-face, presumably by coordination of the OH group to the metal.[11a−d] However all attempts to obtain stereoselective hydrogenation via such a hydroxy-directed hydrogenation failed. We therefore tried another approach (Scheme 5). The chloroacate **7a** was transformed to the

Scheme 5

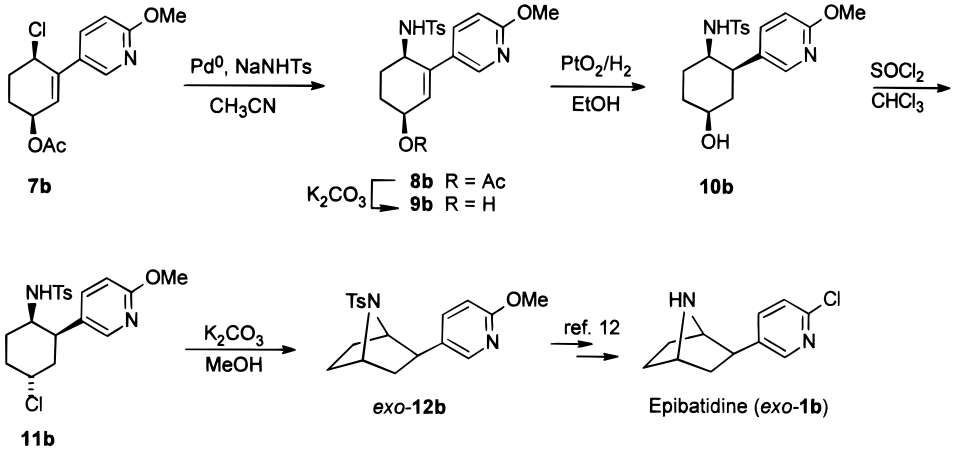


(7) (a) Bai, D.; Xu, R.; Chu, G.; Zhu, X. *J. Org. Chem.* **1996**, *61*, 4600. (b) Xu, R.; Chu, G.; Bai, D. *Tetrahedron Lett.* **1996**, *37*, 1463. (c) Malpass, J. R.; Hemmings, D. A.; Wallis, A. L. *Tetrahedron Lett.* **1996**, *37*, 3911. (d) Trost, B. M.; Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485. (e) Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay, C., Jr.; Temesvári-Major, E.; Blaskó, G. *Tetrahedron* **1996**, *52*, 11053. (f) Zhang, C.; Trudell, M. L. *J. Org. Chem.* **1996**, *61*, 7189. (g) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, P.; Zanirato, V. *Tetrahedron Lett.* **1997**, *38*, 681. (h) Zhang, C.; Gyermek, L.; Trudell, M. L. *Tetrahedron Lett.* **1997**, *38*, 5619. (i) Giblin, G. M. P.; Jones, C. D.; Simpkins, N. S. *Synlett* **1997**, 589. (j) Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1857. (k) Pandey, G.; Bagul, T. D.; Sahoo, A. K. *J. Org. Chem.* **1998**, *63*, 760. (l) Jones, C. D.; Simpkins, N. S.; Giblin, G. M. P. *Tetrahedron Lett.* **1998**, *39*, 1023. (m) Sirisoma, N. S.; Johnson, C. R. *Tetrahedron Lett.* **1998**, *39*, 2059. (n) Clive, D. L. J.; Yeh, V. S. C. *Tetrahedron Lett.* **1998**, *39*, 4789. (o) Aoyagi, S.; Tanaka, R.; Naruse, M.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 4513.

(8) Karlström, S.; Rönn, M.; Thorarensen, A.; Bäckvall, J. E. *J. Org. Chem.* **1998**, 63, 2517.

(9) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492.

Scheme 6



trans-amidoacetate **13a** in 80% yield by reaction with NaNHTs in DMSO at 55 °C. Subsequent hydrolysis afforded the *trans* amido alcohol **14a**. Interestingly, hydrogenation of **14a** with Adams catalyst was highly stereoselective and occurred syn to the NHTs group to produce **15a** with the desired *trans* relationship between nitrogen and phenyl. Mesylation followed by K_2CO_3-promoted cyclization afforded the *N*-tosyl-protected compound *endo*-**12a** in 74% yield from **15a**. The target molecule, *endo*-**1a**, was obtained in 89% yield by removal of the tosyl group.[10]

Synthesis of (±)-Epibatidine (*exo*-1b). The same strategy as for the synthesis of compound *exo*-**1a** was employed for the synthesis of (±)-epibatidine. The amido acetate **8b** was obtained from chloroacetate **7b** in 71% yield using the palladium-catalyzed allylic substitution (Scheme 6). Hydrolysis of **8b** gave amido alcohol **9b**, which was hydrogenated in a highly stereoselective reaction to afford **10b** in 93% yield. Subsequent inversion of the alcohol by the use of thionyl chloride to give **11b** (65% yield) followed by cyclization gave the bicyclic compound *exo*-**12b** (63% yield). The transformation of *exo*-**12b** to epibatidine (*exo*-**1b**) in 53% yield (two steps) has previously been described in the literature.[12]

Conclusion

A stereoselective synthesis of epibatidine and aryl analogues has been developed. The strategy relies on a stereo- and regioselective functionalization of 2-aryl-1,3-cyclohexadienes via the chloroacetoxylation approach[1a] and subsequent stereoselective hydrogenation of the double bond. With this approach both the *exo* and *endo* compounds are accessible.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 400 and 100.6 MHz, respectively. Chemical shifts are reported in ppm with $CDCl_3$ as internal standard (7.26 for ^{1}H and 77.00 ppm for ^{13}C) or methanol (3.49 ppm for ^{1}H or 49.00 ppm for ^{13}C) and coupling constants (*J*) are given in hertz. Assignments of the NMR signals were done using ^{1}H-homo-decoupling, COSY, NOESY, and DEPT experiments. IR spectra were obtained using a Perkin-Elmer 1600 FTIR, and the samples were examined as KBr plates or as thin films on NaBr plates. Peaks are reported in cm^{-1} with the following intensities: s (strong, 67−100%), m (medium, 40−66%), and w (weak, 20−40%). Melting points are uncorrected and were obtained using a Büchi capillary melting point apparatus. Elemental analyses were performed by Analytische Laboratorien, Lindlar, Germany. Diethyl ether, DME, and THF were distilled under nitrogen from sodium benzophenone ketyl. Pyridine and methylene chloride were distilled under nitrogen from calcium hydride. *p*-Toluenesulfonamide monosodium salt[13] (NaNHTs) and tetrakis(triphenylphosphine)palladium[14] were prepared according to known procedures. Thin-layer chromatography (TLC) was run on Merck precoated silica gel 60-F_{254} plates. Progress of reaction was followed by TLC until judged complete for all reactions. For flash chromatography, Merck silica gel 60 (230−400 mesh) was used. 2-Phenyl-1,3-cyclohexadiene (**2a**)[8] and compound **3b**[15] were prepared according to literature procedures.

5-Bromo-2-methoxypyridine (3b).[15] Freshly cut sodium (3.762 g, 163.5 mmol) was dissolved in methanol (40 mL) followed by addition of 2,5-dibromopyridine (12.01 g, 50.71 mmol) in DMF (150 mL). The reaction mixture was stirred for 1 h at 80 °C. Ether (400 mL) was added when the reaction mixture had cooled to room temperature, and the solution was washed with water (4 × 50 mL). The aqueous phase was made basic to pH > 10 using KOH and extracted with ether (2 × 30 mL). The collected organic phases were dried ($MgSO_4$). The solvent was removed in vacuo, and the crude product was separated on silica (ether:pentane 5:95) to yield the title compound (9.05 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (dd, J = 2.5, 0.7 Hz, 1 H, PyH-6), 7.63 (dd, J = 8.8, 2.6 Hz, 1 H,PyH-4), 6.66 (dd, J = 8.8, 0.7 Hz, 1 H, PyH-3), 3.91 (s, 3 H, CH_3O); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.0, 147.5, 141.0, 112.6, 111.7, 53.7.

1-(2-Methoxy-5-pyridyl)-2-cyclohexenol (4b). 5-Bromo-2-methoxypyridine (7.57 g, 40.3 mmol) was dissolved in dry ether (50 mL) and cooled to −78 °C. *n*-Butyllithium (30 mL, 1.56 M in hexanes) was added dropwise over 15 min, and the reaction was stirred at −78 °C for 2 h. 2-Cyclohex-1-one (4.61 g, 48.0 mmol) was added via syringe over 10 min. The reaction was stirred overnight while the temperature was slowly raised to room temperature. Water (50 mL) was added followed by extraction with ether (100 mL) and collection of the organic

(10) Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548.

(11) (a) Thompson, H. W.; McPherson, E.; Lences, B. L. *J. Org. Chem.* **1976**, *41*, 2903. (b) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *106*, 1072. (c) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (d) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

(12) (a) Okabe, K.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1432. (b) Sestanj, K.; Melenski, E.; Jirkovsky, I. *Tetrahedron Lett.* **1994**, *35*, 5417.

(13) Bottini, F.; Di Grazia, M.; Finocchiaro, P.; Fronczek, F. R.; Mamo, A.; Pappalardo, S. *J. Org. Chem.* **1988**, *53*, 3521.

(14) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1990.

(15) Testaferri, L.; Tiecco, M.; Tingoli, M.; Bartoli, D.; Massoli, A. *Tetrahedron* **1985**, *41*, 1373.

phase. The aqueous phase was saturated with NH_4Cl and further extracted with ether (3 × 70 mL). The collected organic phases were dried ($MgSO_4$). The solvent was evaporated and the crude product was directly used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (dt, J = 2.5, 0.6 Hz, 1 H, PyH-6), 7.69 (dd, J = 8.7, 2.6 Hz, 1 H, PyH-4), 6.69 (dm, J = 8.7 Hz, 1 H, PyH-3), 6.01 (ddd, J = 10.0, 4.0, 3.4 Hz, 1 H, olefinic CH), 5.72 (dt, J = 10.0, 2.2 Hz, 1 H, olefinic CH), 3.90 (s, 3 H, CH_3), 2.20 (br s, 1 H, OH), 1.99−2.17 (m, 2 H, allylic CH_2), 1.88−1.98 (m, 1 H, CH_2), 1.70−1.85 (m, 2 H, CH_2), 1.51−1.63 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.2, 144.2, 136.5, 135.8, 131.6, 131.0, 110.1, 70.7, 53.3, 39.4, 24.9, 19.0.

3-(2-Methxoy-5-pyridyl)-2-cyclohexenol (5b). Crude **4b** from the experiment described above was stirred with *p*-TsOH·H_2O (156 mg, 0.820 mmol) in 1,4-dioxane:H_2O 4:1 (80 mL) for 5 h at room temperature. Saturated Na_2CO_3(aq) (40 mL) was added, and the mixture was extracted with ether (3 × 100 mL). The collected organic phases were dried ($MgSO_4$). The solvent was removed in vacuo, and the crude product was purified on silica (ether:pentane gradient 5:95 → 50:50) to yield the title compound (7.52 g, 91% in two steps). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (dt, J = 2.6, 0.6 Hz, 1 H, PyH-6), 7.60 (ddd, J = 8.7, 2.6, 0.5 Hz, 1 H, PyH-4), 6.68 (ddd, J = 8.7, 0.8, 0.4 Hz, 1 H, PyH-3), 6.05 (dddm, J = 3.7, 2.1, 1.7 Hz, 1 H, olefinic CH), 4.33−4.40 (m, 1 H, allylic C*H*OH), 3.84 (s, 3 H, CH_3O), 3.2 (br s, 1 H, OH), 2.39 (dddd, J = 17.5, 6.9, 5.0, 2.0 Hz, 1 H, allylic CH_2), 2.29 (dm, J = 17.5 Hz, 1 H, allylic CH_2), 1.84−1.98 (m, 2 H, CH_2), 1.58−1.79 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.2 (C), 143.2 (CH), 136.1 (C), 135.6 (CH), 129.8 (C), 126.3 (CH), 110.1 (CH), 65.8 (CH), 53.3 (CH_3), 31.3 (CH_2), 26.9 (CH_2), 19.3 (CH_2).

3-(2-Methoxy-5-pyridyl)-2-cyclohexenyl Methyl Carbonate (6b). To a solution of compound **5b** (1.48 g, 7.04 mmol) and pyridine (1.67 g, 21.1 mmol) in CH_2Cl_2 (70 mL) was added methyl chloroformate (1.99 g, 21.1 mmol) over 2 h at 0 °C. The reaction was stirred for an additional 12 h at room temperature. The reaction mixture was washed with water (2 × 100 mL). The organic phase was collected, dried (Na_2SO_4), and concentrated. The crude product was purified on silica (pentane:ether 70:30) to yield the title compound, 1.36 g (72%), as a colorless oil which solidified in the freezer. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20 (dd, J = 2.6, 0.7 Hz, 1 H, PyH-6), 7.63 (dd, J = 8.7, 2.6 Hz, 1 H, PyH-4), 6.70 (dd, J = 8.7, 0.7 Hz, 1 H, PyH-3), 6.07 (ddd, J = 4.0, 1.6, 1.1 Hz, 1 H, olefinic), 5.27−5.33 (m, 1 H, allylic CHO), 3.92 (s, 3 H, CH_3OPy), 3.78 (s, 3 H, CH_3O), 2.43−2.54 (m, 1 H, allylic CH_2), 2.29−2.41 (m, 1 H, allylic CH_2), 1.87−2.02 (m, 3 H, CH_2), 1.74−1.87 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.8 (C), 155.4 (C), 143.7 (CH), 139.8 (C), 135.8 (CH), 129.6 (C), 120.8 (CH), 110.4 (CH), 72.4 (CH), 54.6 (CH_3), 53.5 (CH_3), 27.8 (CH_2), 27.1 (CH_2), 18.9 (CH_2). Anal. Calcd C, 63.87; H, 6.51; N, 5.32; Found: C, 63.96; H, 6.57; N, 5.40.

2-(2-Methoxy-5-pyridyl)-1,3-cyclohexadiene (2b). The allylic methyl carbonate **6b** (800 mg, 3.038 mmol) and Pd(PPh_3)$_4$ (105 mg, 0.091 mmol) were dissolved in THF (7 mL) under argon. The reaction was stirred for 20 h at room temperature and then quenched with sat. Na_2CO_3 (20 mL) and extracted with ether (3 × 40 mL). The combined organic phases were dried (K_2CO_3), evaporated, and purified on silica to give 512 mg (90%) of the title compound. The silica was first deactivated with 2% Et_3N in pentane, and this eluent was used for the separation. About 0.5 mL of 0.02% BHT in pentane was put in each fraction tube before the separation in order to prevent polymerization. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (dd, J = 2.5, 0.8 Hz, 1 H, PyH-6), 7.58 (dd, J = 8.6, 2.5 Hz, 1 H, PyH-4), 6.70 (dd, J = 8.6, 0.8 Hz, 1 H, PyH-3), 6.23 (dq, J = 9.7, 1.8 Hz, 1 H, diene CH-3), 5.98−6.06 (two overlapping m, 2 H, diene CH-4 and CH-1), 3.91 (s, 3 H, CH_3O), 2.27−2.35 (m, 2 H, CH_2-6), 2.16−2.24 (m, 2 H, CH_2-5); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.1 (C), 143.4 (CH), 135.8 (CH), 132.6 (C), 129.5 (C), 128.2 (CH), 125.0 (CH), 122.2 (CH), 110.3 (CH), 53.3 (CH_3), 22.7 (CH_2), 21.8 (CH_2).

***cis*-1-Acetoxy-4-chloro-3-phenyl-2-cyclohexene (7a).** The 2-Phenyl-1,3-cyclohexa-diene (**2a**)[8] (1.58 g, 10.0 mmol dissolved in 4.5 mL of acetone) and LiCl (0.771 g, 18.2 mmol dissolved in HOAc) were added simultaneously over 12 h to a stirred solution of $Pd(OAc)_2$ (0.144 g, 0.64 mmol), LiCl (0.086 g, 2.03 mmol), LiOAc·$2H_2O$ (0.516 g, 5.07 mmol) and *p*-benzoquinone (2.14 g, 20.1 mmol) in a mixture of HOAc (7.0 mL) and acetone (25 mL). After complete addition, the reaction was stirred for another 14 h. The solvents were removed in vacuo, and the residue was diluted with ether (40 mL) and washed with water (2 × 30 mL). The organic layer was washed with 2 M NaOH (3 × 30 mL) and then with water (2 × 30 mL) containing $NaBH_4$ to remove all remaining *p*-benzoquinone. The organic phase was dried over Na_2SO_4 and concentrated to give a yellow oil. The crude product was purified by flash chromatography (pentane:ether 80:20) to yield the title compound, 1.22 g (62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, J = 8.1 Hz, 2 H, aromatic), 7.39−7.32 (m, 3 H, aromatic) 6.06 (d, J = 2.3 Hz, 1 H, olefinic), 5.55−5.50 (m, 1 H, CHOAc), 5.03 (ddd, J = 4.1, 3.1, 1.2 Hz, 1 H, CHCl), 2.37−2.10 (m, 4 H, CH_2) 2.13 (s, 3 H, OAc); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.1 (C), 140.7 (C), 137.9 (C), 128.4 (CH), 128.2 (CH), 127.4 (CH), 126.0 (CH), 69.6 (CH), 54.8 (CH), 30.9 (CH_2), 22.8 (CH_2), 21.2 (CH_3); IR (neat), 3057 (w), 2962 (w), 2909 (w), 2876 (w), 1731 (s), 1662 (w), 1496 (w), 1445 (m), 1374 (m), 1346 (w), 1311 (w), 1266 (s), 1240 (s), 1204 (w), 1084 (w), 1036 (s), 1027 (s), 1000 (w) cm^{-1}.

***cis*-1-Acetoxy-3-phenyl-4-(*p*-toluenesulfonamido)-2-cyclohexene (8a).** To a stirred suspension of Pd(PPh_3)$_4$ (0.074 g, 0.064 mmol), NaNHTs (0.270 g, 1.40 mmol), and H_2NTs (0.099 g, 0.58 mmol) in CH_3CN (3 mL) was added **7a** (0.290 g, 1.15 mmol) dissolved in CH_3CN (1 mL). The reaction was stirred at room temperature for 8 h. The reaction mixture was diluted with EtOAc (30 mL) and washed with brine containing 2% NaOH (3 × 30 mL) and then with water (1 × 30 mL). The organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (pentane: EtOAc 80:20) to give 0.352 g (79%) of **8a** as white crystals, Mp: 175−177 °C (EtOAc:pentane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (dm, J = 8.2 Hz, 2 H, aromatic), 7.19−7.05 (m, 5 H, aromatic), 6.98 (dm, J = 8.6 Hz, 2 H, aromatic), 5.94 (d, 1 H, J = 3.0 Hz, CH olefinic) 5.35−5.32 (m, 1 H, CHOAc), 4.54 (d, J = 6.2 Hz, 1 H, NHTs), 4.25−4.21 (m, 1 H, C*H*NHTs), 2.43 (s, 3 H, CH_3Ar), 2.23−2.21 (m, 1 H, CH_2), 2.09 (s, 3 H, OAc), 2.05−1.97 (m, 1 H, CH_2), 1.88−1.74 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.6 (C), 143.2 (C), 140.1 (C), 137.4 (C), 129.5 (CH), 129.2 (CH), 128.3 (CH), 127.9 (CH), 127.0 (CH), 126.3 (CH), 69.0 (CH), 49.1 (CH), 27.5 (CH_2), 22.7 (CH_2), 21.5 (CH_3), 21.2 (CH_3); IR (KBr), 3250 (s), 3062 (w), 2967 (m), 2937 (m), 2920 (m), 2872 (w), 2728 (w), 2360 (w), 2344 (w), 1732 (s), 1598 (w) cm^{-1}. Anal. Calcd C, 65.43; H, 6.01; N, 3.63; Found: C, 65.23; H, 6.15; N, 3.66.

***cis*-3-Phenyl-4-(*p*-toluenesulfonamido)-2-cyclohexen-1-ol (9a).** To a solution of compound **8a** (2.52 g, 6.53 mmol) in MeOH−H_2O (125 mL, 4:1), was added K_2CO_3 (1.80 g, 13.0 mmol), and the reaction was stirred overnight at room temperature. The MeOH was evaporated, and the residue was diluted with EtOAc (140 mL) and extracted with sat. NH_4Cl (2 × 100 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by flash chromatography (CH_2Cl_2:ether: MeOH 50:50:0.5) to yield 2.086 g (94%) of white crystals. Mp: 155−156 °C (EtOAc/pentane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (dm, J = 8.4 Hz, 2 H, aromatic), 7.20−7.05 (m, 5 H, aromatic), 6.99 (dm, J = 8.0 Hz, 2 H, aromatic), 6.02 (d, J = 2.3 Hz, 1 H, olefinic CH), 4.88 (d, J = 6.3 Hz, 1 H, NHTs), 4.30−4.25 (m, 1 H, allylic C*H*OH), 4.23−4.19 (m, 1 H, C*H*NHTs), 2.42 (s, 3 H, CH_3Ar), 2.19−2.12 (m, 1 H, CH_2), 2.02−1.93 (m, 1 H, CH_2), 1.78−1.63 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.0 (C), 138.1 (C), 138.0 (C), 133.4 (CH) 129.5 (CH), 128.3 (CH), 127.5 (CH), 126.9 (CH), 126.3 (CH), 66.9 (CH), 49.1 (CH), 27.9 (CH_2), 26.4 (CH_2), 21.5 (CH_3); IR (KBr), 3476 (s), 3191 (s), 3065 (w), 3029 (w), 2936 (w), 2868 (w), 1598 (w), 1494 (w), 1445 (m), 1404 (w), 1328 (s), 1315 (s), 1305 (s), 1289 (s), 1153 (s), 1085 (s), 1055 (s), 1030 (w), 1020 (m) 1005 (s) cm^{-1}.

3α-Phenyl-4α-(*p*-toluenesulfonamido)cyclohexane-1α-ol (10a). The amidoalkenol **9a** (2.02 g, 5.90 mmol) was

dissolved in ethanol, and PtO_2 (0.101 g, 0.41 mmol) was added. Hydrogen (1 atm) was applied, and the reaction was stirred at room temperature for 48 h. The catalyst was removed by filtration through Celite, and the solvent was evaporated. The crude product was purified by flash chromatography (EtOAc:pentane 60:40). White crystals were collected, 1.917 g (94%). Mp: 112 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (dm, J = 8.2 Hz, 2 H, aromatic), 7.17−7.10 (m, 3 H, aromatic), 7.02 (dm, J = 8.0 Hz, 2 H,), 6.93 (dm, J = 7.1 Hz, 2 H, aromatic), 4.45 (d, J = 4.7 Hz, 1 H, NHTs), 3.77−3.69 (m, 1 H, C*H*OH), 3.37−3.34 (m, 1 H, C*H*NHTs), 2.87 (ddd, J = 13.6, 3.1, 3.1 Hz, 1 H, PhCH), 2.38 (s, 3 H, CH_3Ar), 2.35−2.29 (m, 1 H, CH_2CHNHTs), 2.07−2.02 (m, 1 H, CH_2), 1.90−1.56 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 142.7 (C), 140.2 (C), 129.4 (CH), 127 (CH), 126.8 (CH), 70.2 (CH), 53.3 (CH), 44.1 (CH), 33.9 (CH_2), 29.8 (CH_2), 21.4 (CH_3); IR (KBr), 3481(s), 3211(m), 2950 (w), 1598 (w). 1497 (w), 1472 (w), 1439 (w), 1315 (s), 1155 (s), 1092 (m), 1047 (s), 1003 (s) cm^{-1}.

1α-Chloro-3*β*-phenyl-4*β*-(*p*-toluenesulfonamido)cyclohexane (11a). To alcohol **10a** (0.040 g, 0.11 mmol), dissolved in $CHCl_3$ (3 mL), was added thionyl chloride (0.5 mL). The reaction was refluxed for 24 h. The solvent was evaporated, the excess of thionyl chloride was evaporated together with toluene (3 × 10 mL), and the crude product was purified by flash chromatography (pentane:EtOAc 80:20) to give 0.028 g (66%) of **11a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22−7.12 (m, 5 H, aromatic), 7.06 (dm, J = 8.2 Hz, 2 H, aromatic), 6.91 (dm, J = 7.0 Hz, 2 H, aromatic), 4.68−4.64 (m, 1 H, CHCl), 4.52 (d, J = 2.0 Hz, 1 H, NHTs), 3.44 (ddd, J = 13.0, 3.6, 3.6 Hz, 1 H, benzylic), 3.39−3.35 (m, 1 H, C*H*NHTs), 2.39 (s, 3 H, CH_3Ar), 2.34−2.12 (m, 4 H, CH_2), 1.90−1.82 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 142.8 (C), 140.1 (C), 135.6 (C), 129.4 (CH), 128.7 (CH), 127.0 (CH), 126.9 (CH), 126.8 (CH), 58.8 (CH), 54.0 (CH), 38.9 (CH), 32.0 (CH_2), 27.5 (CH_2), 25.4 (CH_2), 21.7 (CH_3Ar).

***exo*-2-Phenyl-7-*N*-tosylazabicyclo[2.2.1]heptane (*exo*-12a).** To a stirred solution of **11a** (0.015 g, 0.040 mmol) in methanol (3 mL) was added K_2CO_3 (11 mg, 0.080 mmol). The reaction was stirred at 55 °C for 48 h. The solvent was removed, and the residue was separated on silica (pentane:EtOAc 80:20) to give 0.013 g (95%) of a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 8.2 Hz, 2 H, aromatic), 7.28 (d, J = 8.4 Hz, 2 H, aromatic), 7.20−7.16 (m, 5 H, aromatic), 4.32 (dd, J = 4.3, 3.6 Hz, 1 H, PhCHC*H*), 4.18 (d, J = 3.1 Hz, 1 H, PhCHCH$_2$C*H*), 2.81 (dd, J = 9.0, 5.1 Hz, 1 H, benzylic), 2.43 (s, 3 H, CH_3Ar), 1.99−1.86 (m, 4 H, CH_2), 1.58−1.49 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 144.9 (C), 143.4 (C), 137.8 (C), 129.4 (CH), 128.3 (CH), 127.6 (CH), 127.0 (CH), 126.3 (CH), 65.1 (PhCHCH$_2$CH), 59.4 (PhCHCH), 41.5 (CH_2), 30.1 (CH_2), 29.1 (CH_2), 21.5 (CH_3); IR (CH_2Cl_2), 3055 (w), 2983 (w), 1492 (w), 1455 (w), 1338 (m), 1320 (m), 1304 (w), 1273 (m), 1258 (m), 1223 (w), 1200 (w), 1175 (w), 1152 (s), 1091 (s), 1055 (w), 1031 (w), 1009 (w) cm^{-1}. Anal. Calcd C, 69.69; H, 6.46; N, 4.28; Found: C, 69.54; H, 6.55; N, 4.31.

***exo*-2-Phenyl-7-azabicyclo[2.2.1]heptane (*exo*-1a).** Sodium (0.110 g, 4.78 mmol) and naphthalene (0.780 g, 6.09 mmol) were dissolved in DME under nitrogen. The dark green solution was stirred at room temperature for 2 h. A solution of tosylamide *exo*-**12a** (0.142 g, 0.43 mmol) dissolved in DME (5 mL) was cooled to −60 °C. The sodium naphthalene solution was added dropwise to the tosylamide solution until a dark green solution persisted. The reaction was quenched by addition of sat. $NaHCO_3$ (1 mL). Anhydrous K_2CO_3 (2.2 g) was added, and the solution was stirred for 12 h. The mixture was filtered, and the precipitate was rinsed with CH_2Cl_2:Et_2O (1:1). The organic layer was washed with 2 × 30 mL of 0.5 M HCl (aq). The combined aqueous phase was washed with CH_2Cl_2 and Et_2O. The aqueous phase was made alkali with 1 M KOH (aq) and then extracted with 2 × 30 mL of CH_2Cl_2:Et_2O (1:1). The organic layer was dried (Na_2SO_4) and concentrated to give 0.074 g (97%) of *exo*-**1a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.28 (m, 4 H), 7.20−7.16 (m, 1 H), 3.78 (dd, J = 4.4, 3.6 Hz, 1 H, PhCHC*H*), 3.62 (d, J = 3.9 Hz, 1 H, PhCHCH$_2$C*H*), 2.88 (dd, J = 8.8, 5.4 Hz, 1 H, benzylic), 1.95−1.90 (m, 1 H), 1.76−1.43 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 146.3 (C), 128.3 (CH), 127.0 (CH), 125.8 (CH), 62.8 (CH), 56.4 (CH), 48.0 (CH), 40.1 (CH_2), 30.8 (CH_2), 29.6 (CH_2); IR (film), 3064 (w), 3027 (w), 2966 (s), 2927 (s), 2874 (m), 2253 (m), 1496 (w), 1202 (w), 1053 (w) cm^{-1}.

***trans*-1-Acetoxy-3-phenyl-4-(*p*-toluenesulfonamido)-2-cyclohexene (13a).** The chloroacetate **7a** (1.43 g, 5.70 mmol) was added to stirred solution of NaNHTs (1.65 g, 8.55 mmol) and H_2NTs (0.488 g, 2.85 mmol) in DMSO (25 mL). The reaction mixture was heated at 55 °C for 24 h. After cooling, the mixture was diluted with EtOAc (100 mL) and washed with brine containing 2% NaOH (3 × 70 mL) and sat. NH_4Cl (75 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified on silica (pentane:EtOAc gradient 90:10 → 40:60) which afforded 1.76 g (80%) of white crystals. mp: 135 °C (CH_2Cl_2:pentane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (dm, J = 8.2 Hz, 2 H, aromatic), 7.25−7.15 (m, 3 H, aromatic), 7.04−7.15 (m, 2 H, aromatic), 6.98 (dm, J = 8.0 Hz, 2 H), 6.06 (d, J = 4.4 Hz, 1 H, olefinic), 5.35 (app t. dd, J = 8.1, 4.2, 4.2 Hz, 1 H, CHOAc), 4.36 (d, J = 5.7 Hz, 1 H, HNTs), 4.32−4.28 (m, 1 H, C*H*NHTs), 2.43 (s, 3 H, CH_3Ar), 2.07−1.98 (m, 2 H, CH_2), 2.00 (s, 3 H, OAc), 1.80−1.78 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.5 (C), 143.2 (C), 141.4 (C), 137.6 (C), 136.9 (C), 129.5 (CH), 128.4 (CH), 128.1 (CH), 127.4 (olefinic), 127.1 (CH), 126.4 (CH), 66.9 (CH), 49.3 (CH), 26.1 (CH_2), 23.3 (CH_2), 21.5 (CH_3), 21.1 (CH_3); IR (KBr), 3232 (s), 3019 (w), 2973 (w), 2940 (w), 2867 (w), 1741 (s), 1492 (w), 1450 (m), 1373 (s), 1329 (s), 1300 (w), 1289 (m), 1260 (s), 1200 (m), 1182 (m), 1155 (s), 1120 (m), 1089 (s), 1008 (s) cm^{-1}.

***trans*-3-Phenyl-4-(*p*-toluenesulfonamido)-2-cyclohexen-1-ol (14a).** To a solution of **13a** (0.590 g, 1.53 mmol) in MeOH:H_2O (13 mL, 4:1) was added K_2CO_3 (0.221 g, 1.60 mmol), and the reaction was stirred overnight at room temperature. White crystals were formed during the reaction which were filtered off and collected. The methanol was evaporated, and the remaining crude product was recrystallized from methanol/H_2O to give 0.473 g (90%) of white crystals. Mp: 190−192 °C (MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (dm, J = 8.2 Hz, 2 H, aromatic), 7.15−7.22 (m, 3 H, aromatic), 7.04−7.13 (m, 2 H, aromatic), 6.97 (d, J = 7.2 Hz, 2 H, aromatic), 6.07 (d, J = 4.1 Hz, 1 H, olefinic), 4.36−4.32 (m, 1 H, C*H*OH), 4.29−4.24 (m, 2 H, overlapping N*H*Ts and C*H*NHTs), 2.44 (s, 3 H, CH_3-Ar), 2.14−1.98 (m, 3 H, CH_2), 1.75−1.68 (m, 1 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.3 (C), 139.6 (C), 138.0 (C), 137.0 (C), 131.5 (CH), 129.1 (CH), 128.4 (CH), 127.9 (C), 127.1 (CH), 126.5 (CH), 64.7 (CH), 49.7 (CH), 27.0 (CH_2), 26.1 (CH_2), 21.5 (CH_3); IR (KBr), 3518 (s), 3250 (s), 2966 (m), 2927 (m), 1598 (w), 1492 (w), 1438 (m), 1292 (m), 1251 (m), 1155 (s), 1097 (m), 1015 (s) cm^{-1}.

3α-Phenyl-4*β*-(*p*-toluenesulfonamido)cyclohexane-1α-ol (15a). The amidoalkenol (0.587 g, 1.72 mmol) was dissolved in ethanol (15 mL). PtO_2 was added, and H_2 (1 atm) was introduced. The reaction was stirred at room temperature for 78 h. The catalyst was filtered off, and solvent was removed. The crude product was purified on silica (pentane:EtOAc gradient 90:10 → 20:80) to give 0.510 g (86%) of a white solid. Mp: 185 °C (EtOAc:pentane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (dm, J = 8.2 Hz, 2 H, aromatic), 7.16−7.07 (m, 5 H, aromatic), 6.84 (dm, J = 7.0 Hz, 2 H, aromatic), 4.22 (d, J = 7.0 Hz, 2 H, NHTs) 3.75−3.67 (m, 1 H, C*H*OH), 3.07−2.99 (m, 1 H, C*H*NHTs), 2.49−2.40 (m, 1 H, benzylic), 2.42 (s, 3 H, CH_3-Ar), 2.09−2.01 (m, 2 H), 1.60−1.40 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 142.9 (C), 140.7 (C), 136.5 (C), 129.4 (CH), 128.9 (CH), 69.5 (CH), 56.6 (CH), 48.3 (CH), 42.8 (CH_2), 33.9 (CH_2), 32.2 (CH_2), 21.5 (CH_3); IR (KBr), 3494 (s), 3236 (s), 3059 (m), 3031 (w), 2928 (s), 2852 (m), 1496 (m), 1452 (m), 1406 (m), 1309 (s), 1281 (s), 1248 (w), 1210 (w), 1189 (w), 1160 (s), 1078 (s), 1060 (s), 1019 (w) cm^{-1}. Anal. Calcd C, 66.06; H, 6.71; N, 4.05; Found: C, 66.02; H, 6.78; N, 4.10.

1α-(Mesyloxy)-3α-phenyl-4*β*-(*p*-toluenesulfonamido)-cyclohexane (16a). Methanesulfonyl chloride (0.040 g, 0.34 mmol) was added dropwise, at 0 °C, to a stirred solution of Et_3N (0.032 g, 0.32 mmol) and **15a** in THF (3 mL). After complete addition, the reaction was stirred for 12 h, 0 °C → rt. The reaction was quenched with ice/water, and the mixture

was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude product was directly used in the next step.

***endo*-2-Phenyl-7-*N*-tosylazabicyclo[2.2.1]heptane (*endo*-12a).** The crude mesylate **16a** was dissolved in methanol (3 mL), and K_2CO_3 (0.047 g, 0.35 mmol) was added. The reaction was heated at 55 °C for 48 h. The solvent was removed, and the crude product was separated on silica (pentane:ether 80:20) to give 0.056 g (74%, based on **15a**) of a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (dm, J = 8.2 Hz, 2 H, aromatic), 7.22 (m, 1 H, aromatic), 7.16 (dm, J = 7.8 Hz, 2 H, aromatic), 4.35 (dd, J = 4.4, 4.4 Hz, 1 H, PhCHC*H*), 4.28 (dd, J = 4.8, 4.8 Hz, 1 H, PhCHCH$_2$C*H*), 3.60 (ddd, J = 11.7, 5.5, 4.5 Hz, 1 H, benzylic), 2.43 (s, 3 H, CH_3Ar), 2.29 (tdd, J = 12.1, 5.2, 3.2 Hz, 1 H, PhCHC*H*$_2$ *exo*), 1.86−1.76 (m, 1 H, CH_2), 1.65 (dd, J = 12.4, 5.6 Hz, 1 H, PhCHC*H*$_2$ *endo*), 1.39−1.59 (m, 3 H, C*H*$_2$); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.4 (C), 139.3 (C), 137.9 (C), 129.4 (CH), 128.4 (CH), 128.0 (CH), 127.5 (CH), 126.5 (CH), 63.6 (CH), 60.4 (CH), 46.9 (CH), 34.6 (CH_2), 30.6 (CH_2), 23.8 (CH_2), 21.5 (CH_3); IR (CH_2Cl_2), 2956 (w), 2922 (w), 1598 (w), 1496 (w), 1471 (w), 1454 (w), 1401 (w), 1349 (s), 1319 (m), 1303 (m), 1153 (s), 1096 (s), 1052 (m), 1041 (m) cm^{-1}.

***endo*-2-Phenyl-7-azabicyclo[2.2.1]heptane (*endo*-1a).** The deprotection was performed as described for compound *exo*-**12a** to yield *endo*-**1a** (0.021 g, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.28 (m, 2 H), 7.22−7.17 (m, 3 H), 3.78 (dd, J = 4.9, 4.4 Hz, 2 H), 3.40−3.36 (m, 1 H), 2.94 (broad s, 1 H), 2.12−2.04 (m, 1 H), 1.70−1.55 (m, 2 H), 1.46−1.35 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 140.9 (C), 128.2 (CH), 128.0 (CH), 126.1 (CH), 61.5 (CH), 57.8 (CH), 47.5 (CH), 34.5 (CH_2), 30.7 (CH_2), 29.7 (CH_2); IR (film), 3369 (m), 2959 (s), 2364 (w), 1736 (w), 1601 (m), 1497 (m), 1458 (m), 1376 (m), 1121 (w), 914 (w) cm^{-1}.

***cis*-1-Acetoxy-4-chloro-3-(2-methoxy-5-pyridyl)-2-cyclohexene (7b).** To a suspension of $Pd(OAc)_2$ (18 mg, 0.082 mmol), LiCl (14 mg, 0.326 mmol), *p*-benzoquinone (176 mg, 1.63 mmol), and LiOAc·2H_2O (42 mg, 0.408 mmol) in HOAc (0.3 mL) and acetone (1.3 mL) were simultaneously added over 15 h (i) LiCl (55 mg, 1.30 mmol) in HOAc (0.5 mL) and acetone (0.3 mL) and (ii) diene **2b** (152 mg, 0.815 mmol) in acetone (0.8 mL). The reaction was stirred for another 21 h. Ether (50 mL) was added followed by sat. Na_2CO_3 until the pH of the aqueous phase was above 8. After extraction, the ether phase was collected, and the aqueous phase was further extracted with ether (3 × 50 mL). The combined organic phases were washed with 2 M NaOH (3 × 40 mL) and brine (30 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was separated on silica (ether:pentane 1:4) to yield the title compound (69 mg, 30%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27 (dm, J = 2.6 Hz, 1 H, PyH-6), 7.68 (dd, J = 8.7, 2.6 Hz, 1 H, PyH-4), 6.73 (dd, J = 8.7, 0.8 Hz, 1 H, PyH-3), 5.99 (dd, J = 2.6, 0.9 Hz, 1 H, olefinic CH), 5.47−5.54 (m, 1 H, CHO), 4.90−4.95 (m, 1 H, CHCl), 3.95 (s, 3 H, CH_3O), 2.34 (ddd, J = 14.5, 6.9, 3.3 Hz, 1 H, CH_2), 2.12 (s, 3 H, CH_3C(O)), 1.89−2.29 (m, 3 H, CH_2); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.7 (C), 164.0 (C), 144.6 (CH), 137.9 (C), 136.4 (CH), 127.0 (CH), 126.9 (C), 110.6 (CH), 69.6 (CH), 54.6 (CH), 53.6 (CH_3), 30.8 (CH_2), 22.8 (CH_2), 21.3 (CH_3).

***cis*-1-Acetoxy-3-(2-Methoxy-5-pyridyl)-4-(*p*-toluenesulfonamido)-2-cyclohexene (8b).** To a stirred suspension of $Pd(PPh_3)_4$ (0.115 g, 0.1 mmol), NaNHTs (0.468 g, 2.4 mmol), and H_2NTs (0.171 g, 1.0 mmol) in CH_3CN (4 mL), under argon, was added **7b** (0.569 g, 2.0 mmol) in CH_3CN (4 mL). The reaction was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc (70 mL) and washed with brine containing 2% NaOH (3 × 50 mL). The combined organic layer were dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (pentane:EtOAc 2:1) to give 0.590 g (71%) of white sticky crystals. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, J = 2.3 Hz, 1 H, pyH-6), 7.49 (d, J = 8.2 Hz, 2 H, aromatic), 7.15−7.11 (m, 3 H, aromatic), 6.37 (d, J = 8.5 Hz, 1 H, pyH-3), 5.82 (d, J = 2.6 Hz, 1 H, olefinic), 5.29−5.25 (m, 1 H, CHOAc), 4.96 (d, J = 7.3 Hz, 1 H, NHTs), 4.16−4.14 (m, 1 H, C*H*NHTs), 3.89 (s, 3 H, CH_3O), 2.39 (s, 3 H, C*H*$_3$Ar), 2.04 (s, 3 H, OAc), 1.98−1.93 (m, 2 H), 1.82−1.64 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.5 (C), 163.6 (C), 144.8 (CH), 143.3 (C), 137.33 (C), 137.27 (C), 136.0 (CH), 129.5 (CH), 128.7 (CH), 126.8 (CH), 126.8 (CH), 110.1 (CH), 68.7 (CH), 53.4 (CH_3), 49.1 (CH), 27.5 (CH_2), 22.6 (CH_2), 24.1 (CH_3), 21.1 (CH_3); IR (KBr) 1727, 1289, 1161 cm^{-1}.

***cis*-3-(2-Methoxy-5-pyridyl)-4-(*p*-toluenesulfonamido)-2-cyclohexen-1-ol (9b).** Compound **8b** (0.350 g, 0.84 mmol) was dissolved in a mixture of MeOH:water (4:1, 8 mL), K_2CO_3 was added, and the reaction was stirred overnight at room temperature. The solvents were evaporated, and the residue was purified on silica (EtOAc:pentane 4:1) to give 0.253 g (81%) of white crystals. Mp: 158−159 °C ($CHCl_3$:pentane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, J = 2.3 Hz, 1 H, pyH-6), 7.51 (d, J = 8.2 Hz, 2 H, aromatic), 7.17−7.12 (m, 3 H, aromatic), 6.38 (d, J = 8.7 Hz, 1 H, pyH-3), 5.93 (d, J = 2.6 Hz, 1 H, olefinic), 5.22 (d, J = 7.5 Hz, 1 H, NHTs), 4.27−4.22 (m, 1 H, allylic CHOH), 4.16−4.13 (m, 1 H, C*H*NHTs), 3.90 (s, 3 H, CH_3O), 2.42 (s, 3 H, C*H*$_3$Ar), 2.07−1.93 (m, 2 H), 1.76−1.58 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.6 (C), 144.8 (CH), 143.3 (CH), 137.4 (CH), 136.4 (CH), 135.3 (C), 133.13 (CH), 129.5 (CH), 127.3 (C), 126.8 (CH), 110.2 (CH), 66.7 (CH), 53.5 (CH_3), 49.2 (CH), 27.9 (CH_2), 26.4 (CH_2), 21.5 (CH_3); IR (KBr), 1330, 1289 cm^{-1}.

3α-(2-Methoxy-5-pyridyl)-4α-(*p*-toluenesulfonamido)-cyclohexane-1α-ol (10b). The amidoalkenol **9b** (0.050 g, 0.13 mmol) was dissolved in EtOH (5 mL). PtO_2 was added, and H_2 (1 atm) was introduced. The reaction was stirred at room temperature for 5 d, filtered through Celite, and the solvent was removed. The crude product was purified by flash chromatography (EtOAc) to give 0.047 g (93%) of white crystals. Mp: 223 °C ($CHCl_3$:pentane). ^{1}H NMR (CD_3OD, 400 MHz) δ 7.75 (d, J = 2.4 Hz, 1 H,pyH-6), 7.32−7.27 (m, 3 H, aromatic), 7.06 (d, J = 8.1 Hz, 2 H, aromatic), 6.38 (d, J = 8.5 Hz, 1 H, pyH-3), 3.86 (s, 3 H, CH_3O), 3.64−3.62 (m, 1 H, C*H*OH), 3.49 (dd, J = 5.4, 2.5 Hz, 1 H, C*H*NHTs), 2.83−2.78 (m, 1 H, pyr-C*H*) 2.38 (s, 3 H, CH_3Ar), 1.89−1.77 (m, 4 H), 1.72−1.63 (m, 2 H); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 164.2 (C), 146.3 (CH), 143.8 (C), 139.9 (CH), 139.6 (C), 131.6 (C); 130.3 (CH), 127.5 (CH), 111.0 (CH), 70.8 (CH), 54.8 (CH), 54.0 (CH_3), 42.8 (CH), 35.0 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 21.4 (CH_3); IR (KBr), 1338, 1290, 1157, 1093 cm^{-1}. Anal. Calcd C, 60.62; H, 6.43; N, 7.44; Found: C, 60.51; H, 6.49; N, 7.49.

1α-Chloro-3β-(2-Methoxy-5-pyridyl)-4β-(*p*-toluenesulfonamido)cyclohexane (11b). To a stirred solution of **10b** was added thionyl chloride, and the reaction was refluxed for 8 h. After being cooled to room temperature, the reaction was quenched with ice, diluted with sat. $NaHCO_3$, and extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$), concentrated, and purified by flash chromatography (pentane:EtOAc 1:1) to give 0.020 g (65%) of white crystals. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, J = 2.3 Hz, 1 H, pyrH-6), 7.32 (d, J = 8.24 Hz, 1 H, aromatic), 7.09−7.04 (m, 3 H, aromatic), 6.39 (d, J = 8.5 Hz, 1 H, pyrH-3), 4.68−4.64 (two overlapping m, 2 H, CHCl and NHTs), 3.91 (s, 3 H, CH_3O), 3.43−3.72 (m, 1 H, C*H*NHTs), 3.35 (ddd, J = 13.0, 3.4, 3.4 Hz, 1 H, pyr-CH), 2.40 (s, 3 H, CH_3Ar), 2.24−1.85 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.0 (C), 144.9 (CH), 143.2 (C), 137.6 (CH), 129.4 (CH), 128.5 (C), 126.7 (CH), 110.7 (CH), 58.4 (CH), 53.8 (CH), 53.3 (CH_3), 36.4 (CH), 32.0 (CH_2), 27.4 (CH_2), 26.1 (CH_2), 21.4 (CH_3); IR(film) 1320, 1294, 1156 cm^{-1}.

***exo*-2-(2-Methoxy-5-pyridyl)-7-*N*-tosylazabicyclo[2.2.1]-heptane (*exo*-12b).** To a stirred solution of **11b** (0.010 g, 0.027 mmol) in MeOH (2 mL) was added K_2CO_3 (0.018 g, 0.14 mmol). The reaction was stirred at 55 °C for 7 d. The solvent was evaporated, and the crude product was purified by flash chromatography (pentane:EtOAc 60:40) to give 0.006 g (63%) of white crystals. The NMR data was identical with the compound described in the literature.[12b]

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds *exo*-**1a**, *endo*-**1a, 5b, 6b, 7a**, **7b**, **8a**, **8b**, **9a**, **9b**, **10a**, **10b**, **11a**, **11b**, *exo*-**12a**, *exo*-**12b**, *endo*-**12a**, **13a**, **14a**, and **15a** (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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