A New Approach to (−)-Swainsonine by Ruthenium-Catalyzed Ring Rearrangement

Nicole Buschmann, Anke Rückert, and Siegfried Blechert*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, D-10623 Berlin, Germany

blechert@chem.tu-berlin.de

Received February 4, 2002

A new enantioselective synthesis of the idolizidine alkaloid (−)-swainsonine **1** in 40% overall yield starting from the known oxazolidinone **6** is described. Throughout the synthesis, the high efficiency of metal-catalyzed reactions is illustrated. The key step is a new ruthenium-catalyzed metathesis rearrangement reaction. In this ring-closing/ring-opening tandem process, stereocenters are transferred from a ring to the olefinic side chain of the formed heterocycle. The metathesis precursor was obtained by palladium-catalyzed desymmetrization of cyclopentenediol. The synthesis was completed by functionalization of the terminal double bond, cyclization of the second ring, and diastereoselective dihydroxylation.

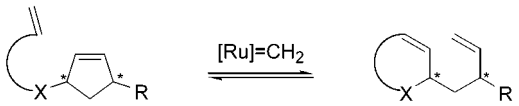
Introduction

During the past decade, the synthetic potential of ring-closing metathesis (RCM) as a mild and catalytic C−C bond-forming method has been well recognized.[1] RCM is widely used in the synthesis of small, medium, and large rings. However, the application of RCM to the synthesis of chiral carbo- or heterocycles is often limited by the accessibility of the chiral acyclic precursor dienes. To avoid complicated multistep syntheses of such chiral acyclic dienes, a new concept for the synthesis of chiral carbo- and heterocycles—a ring rearrangement domino process —has recently been developed.[2] In these ruthenium-catalyzed metathesis reactions a carbocycle is transformed into a heterocyclic product by an intramolecular ring-closing/ring-opening domino metathesis (Scheme 1).

Due to the reversibility of the metathesis cycloaddition/cycloreversion sequences of the rearrangement, the reaction is thermodynamically controlled. The ratio of starting material to rearrangement product is therefore determined by the difference of free energy of formation of product and reactant.

The ring-rearrangement reaction of chiral carbocycles, e.g., cyclopentene derivatives, offers significant advantages over RCM methodology. Enantiomerically pure cyclopentene precursors are readily accessible in contrast to chiral acyclic dienes. The palladium-catalyzed allylic substitution of cyclopentene derivatives offers one possibility for the synthesis of such carbocycles.[3] In the metathesis rearrangement, a stereocenter is transferred from the carbocycle into the side chain of the formed heterocycle, thus incorporating the desired chiral moieties into the product (Scheme 1).

Scheme 1. Ruthenium-Catalyzed Ring Rearrangement



We recently applied the ruthenium-catalyzed ring rearrangement in the synthesis of (−)-halosaline[2b] and (+)-dumetorine. Herein, we report a ruthenium-catalyzed ring rearrangement of a chiral cyclopentene precursor and demonstrate the efficiency of this flexible concept in the synthesis of the polyhydroxylated indolizidine alkaloide (−)-swainsonine **1**. Swainsonine was first isolated from the fungus *Rhizoctonia leguminicolain*[4] in 1973 and has since attracted great attention from both biological and synthetic points of view.[5] It is found to be an effective inhibitor of α-D-mannosidases, including the glycoprotein-processing enzyme mannosidase II.[6] It also exhibits important antimetastatic, antitumor-proliferative, anticancer, and immunoregulating activity.[6] Swainsonine was the first inhibitor to be selected for testing as an anticancer drug, reaching phase I clinical trials. Due to its promising biological profile, much effort has been devoted to the development of efficient syntheses of this azasugar analogue.[7]

Retrosynthetic analysis reveals that the target molecule **1** may arise from functionalized dihidropyrrolidine

* To whom correspondence should be addressed. Tel: +49-30-31422255. Fax: +49-30-31423619.

(1) For recent reviews, see: (a) Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140−3172; *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450. (c) Armstrong, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 317−388. (d) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37−72. (e) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124−2144; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056.

(2) For examples, see: (a) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584−9591. (b) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179−8188. (c) Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 1828−1829.

(3) (a) Trost, B. M.; Patterson, D. E. *J. Org. Chem.* **1998**, *63*, 1339−1341. (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (c) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343.

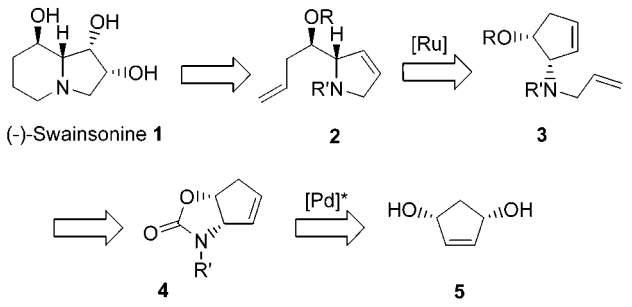
(4) Guengerich, F. P.; DiMari, S. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1973**, *95*, 2055−2056.

(5) For a review concerning synthesis and biological activity of swainsonine and other glycosidase inhibitors, see: Nishimura, Y. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1992; Vol. 10, pp 495−583.

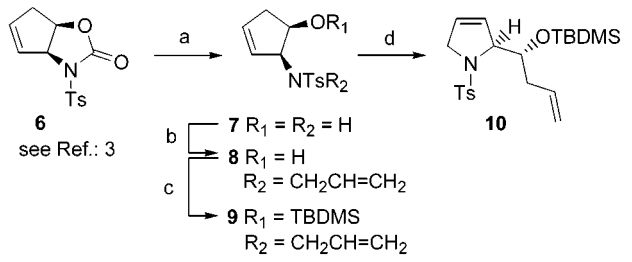
(6) For a recent review, see: El Nemr, A. *Tetrahedron* **2000**, *56*, 8579−8629.

10.1021/jo025589u CCC: $22.00
Published on Web 05/15/2002

Scheme 2. Retrosynthetic Analysis



Scheme 3. Reagents and Conditions[a]



[a] Key: (a) KOH, MeOH, 70 °C, 60 min, 98%; (b) CH_2=$CHCH_2Br$, K_2CO_3, DMF, rt, 12 h, 99%; (c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 98%; (d) 5 mol % ($Cl_2(PCy_3)_2RuCHPh$ (Cy = cyclohexyl)), CH_2=CH_2, CH_2Cl_2, 40 °C, 1 h, 98%.

2, which itself could be readily prepared via a ruthenium-catalyzed ring rearrangement as the key step in our synthetic strategy. The metathesis precursor **3** is readily available by asymmetric palladium-catalyzed allylic amination of *meso*-diol **5** (Scheme 2). Unlike most synthetic approaches using starting materials from the chiral pool, both enantiomers of **4** would be available by this strategy.

Results and Discussion

An enantiomerically pure oxazolidinone derivative **6** serves as the initial chiral material in our synthesis (Scheme 3). The efficiency of palladium-catalyzed desymmetrization of *meso*-bis-carbamate substrates, which can be generated in situ by reaction of a diol with 2 equiv of *p*-tosyl isocyanate, has been demonstrated by Trost.[3] Oxazolidinone derivative **6** was prepared on large scale, using in situ generated bis-carbamate of **5**, 3 equiv of NEt_3, and 2.5 mol % of the chiral palladium catalyst at −50 to 0 °C. The catalyst was prepared from ligand L* = (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenyphosphinobenzoyl) and tris(dibenzylideneacetone)-dipalladium(0) choroform complex in THF. HPLC analysis revealed an enantiomeric excess (ee) of the corresponding oxazolidinone **6** of greater than 97%. Recrystallization from dichlormethane/hexanes increased the ee to >99%. The metathesis precursor **9** was then obtained in high yield by a standard sequence of carbamate hydrolysis, amide alkylation, and protection of the secondary alcohol as TBDMS ether in 95% overall yield.

As shown in Scheme 3, the ruthenium-catalyzed metathesis successfully converted **9** into the desired dihydropyrrole **10**. Correlating well with previous findings,[2b] the sterically demanding TBDMS ether proved to be essential to shift the rearrangement equilibrium completely toward the product. In contrast, rearrangement of the benzyl ether analogue of **9** afforded an starting material/product ratio of 18:1. We would propose that the superiority of the TBDMS group is due to increased steric interactions between substituents, thus facilitating ring opening. In addition, dimerization of products could be suppressed by introduction of this large substituent on the hydroxy group. Excess ethylene as an additive in the metathesis increased the yield and avoided side product formation.[2b] When the reaction was performed with a 0.05 M concentration of **9** in CH_2Cl_2 using 5 mol % of the commercially available "Grubbs' catalyst" (benzylidene-bis-(tricyclohexylphosphine)ruthenium dichloride) and excess ethylene, an isolated yield of up to 98% was achieved. When the amount of catalyst was reduced to 1 mol %, the isolated yield decreased to 89%. For the essential removal of all ruthenium impurities from the product,[8] 1.5 equiv (relative to the amount of Grubb's catalyst) of lead tetraacetate was added to the reaction mixture after complete conversion of **9**. Subsequent filtration of the reaction mixture through a pad of silica gel and washing with CH_2Cl_2 yielded the desired product **10** as a colorless solid. Stereochemical integrity of the two chiral centers was completely preserved in this rearrangement.

For the formation of the six-membered ring system, the terminal double bond needed to be functionalized appropriately (Scheme 4). Selective hydroboration with 9-BBN followed by oxidative workup with $NaOH/H_2O_2$ provided the terminal alcohol. If the rearrangement product **10** was simply chromatographed without using lead tetraacetate to remove all traces of ruthenium, these remaining impurities lead to no conversion in the hydroboration. Decomposition of starting material was observed. Subsequent deprotection of the tosyl group was accomplished by using freshly prepared sodium amalgam in methanolic phosphate buffer without isolation of the secondary amine.[9] All attempts to induce cyclization by in situ activation of the terminal alcohol were unsuccessful. Therefore, the amine was selectively protected as the allyl carbamate by treatment of the crude detosylated product with allyl chloroformate and sodium hydroxide in CH_2Cl_2/H_2O. Subsequent mesylation of the primary alcohol provided the cyclization precursor **13**. The allyl oxycarbonyl group was then deprotected by polymer-bound $Pd(PPh_3)_4$, and subsequent nucleophilic substitution of the mesylate by the freed amino group provided indolizidine derivative **14** in 95% yield after simple filtration through basic alumina. The utilization of soluble $Pd(PPh_3)_4$ was not feasible, since the indolizidine derivative **14** was not stable after chromatography using silica gel. Decomposition took place within a few hours.

With the indolizidine derivative **14** now established, only the surprisingly nontrivial oxidation of the alkene remained to complete the synthesis. Introduction of the *cis*-dihydroxy functionality in the 1- and 2-positions of **14** was planned to be carried out according to the procedure of Mukai et. al., who reported a selectivity of 88:12 in favor of the desired configuration using OsO_4, NMO, acetone, and water at room temperature.[10] How-

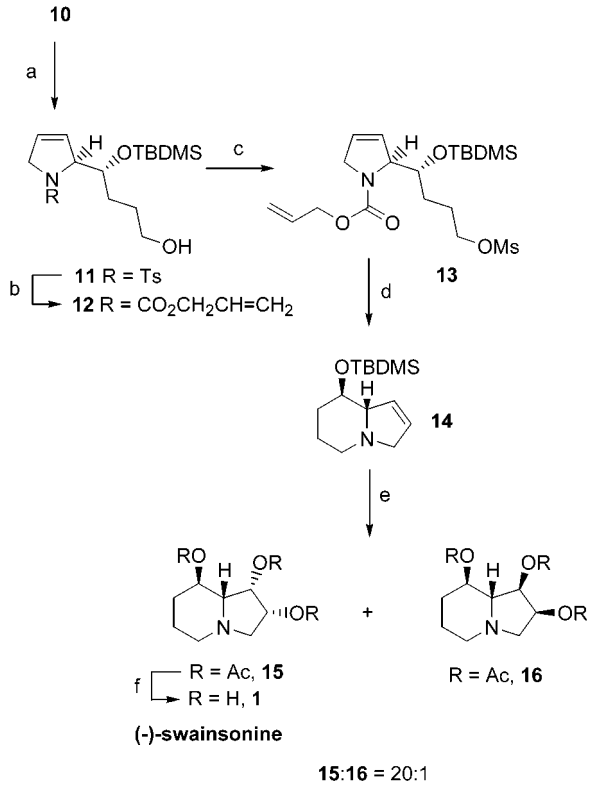
(7) For some recent syntheses of (−)-swainsonine, see: (a) Zhao, H.; Hans, S.; Cheng, X.; Mootoo, D. R. *J. Org. Chem.* **2001**, *66*, 1761−1767. (b) de Vicente, J.; Arrayas, R. G.; Canada, J.; Carretero, J. C. *Synlett* **2000**, 53−56, (c) Trost, B. M.; Patterson, D. E. *Chem. Eur. J.* **1999**, *5*, 3279−3284.

(8) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Mendez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259−1261.

(9) Chavez, F., Sherry, A. D. *J. Org. Chem.* **1989**, *54*, 2990−2992.

(10) Mukai, C.; Sugimoto, Y.; Miyazawa, K.; Yamaguchi, S.; Hanaoka, M. *J. Org. Chem.* **1998**, *63*, 6281−6287.

Scheme 4[a]



[a] Reagents and conditions: (a) (i) 9-BBN, THF, 0−55 °C, 8 h, (ii) $NaOH/H_2O_2$, EtOH, 60 min, reflux, 83%; (b) (i) Na/Hg, MeOH, reflux, 120 min, (ii) NaOH, CH_2=$CHCH_2CO_2Cl$, CH_2Cl_2/H_2O, rt, 60 min, 89%; (c) MsCl, NEt_3, CH_2Cl_2, 0 °C, 2 h, 98%; (d) Pd^0, NEt_3, dimedone, THF, 3 h, rt, 3 h 60 °C, 95%; (e) (i) AD-mix-α, $CH_3SO_2NH_2$, 5 °C, 1 week, (ii) TBAF, THF, rt, 24 h, (iii) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 24 h, 68% (**13**:**14** = 20:1); (f) Amberlite IRA-401, MeOH, rt, 2 h, 96%.

ever, in our hands, these results could not be reproduced. Unfortunately, after desilylation and described protection as triacetates, we observed almost no diastereoselectivity (ratio of **15**/**16** = 50:50−42:58).[11]

To improve the facial selectivity of the dihydroxylation reaction an asymmetric oxidation was employed.[12] With use of AD-mix-α, the stereoselectivity of the syn-hydroxylation was improved, leading to a 20:1 mixture of diastereomeric diols favoring the desired diastereomer. Dihydroxylation occurred mainly from the face of the double bond in a trans relationship with regard to H8a. Since this mixture of diastereomers could not be separated by column chromatography, the mixture was desilylated and converted into the corresponding triacetates **15** and **16**.[10] Column chromatography provided **15** (318 mg) and **16** (6 mg) in 65% and 3% yield. Comparison of spectroscopic data with those previously reported in the literature for the triacetate of natural (−)-swainsonine **1** and the triacetate of 1,2-di-*epi*-swainsonine **16** confirmed their stereochemical assignments. Finally, basic hydrolysis of **15** using Amberlite resin (Amberlite IRA-401) in methanol at room temperature provided (−)-swainsonine **1** in 96% isolated yield.

(11) A diastereomeric ratio of 20:80 (favoring the undesired configuration) was recently reported using the even more bulky TIPS protecting group on the C8 oxygen; see ref 7b.

(12) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

Conclusion

In summary, the concept of ring-closing/ring-opening tandem metathesis was successfully applied to the synthesis of the polyhydroxylated indolizidine alkaloid (−)-swainsonine **1**, which was obtained in 40% yield over 12 steps starting from **6**. Our strategy enables the synthesis of enantiomerically pure heterocycles carrying a functionalized side chain amenable to further manipulations.

Experimental Section

General Methods. All reagents were obtained commercially and were used without further purification. All reactions were carried out under an inert atmosphere (N_2) unless otherwise indicated. Anhydrous tetrahydrofuran was obtained by distillation from sodium benzophenone, dichlormethane from calcium hydride, and methanol from magnesium. The enantiomeric excesses were determined by chiral HPLC analyses with a CHIRACEL OJ column using hexane/isopropyl alcohol mixtures as eluent.

(3a*S*,6a*R*)-3-(Toluene-4-sulfonyl)-3,3a,6,6a-tetrahydrocyclopent-4-enoxazol-2-one (6). To a solution of the *meso*-diol **5** (7.00 g, 69.92 mmol) in 120 mL of THF was added tosyl isocyanate (34.45 g, 174.67 mmol) at room temperature. The mixture was then stirred at 60 °C for 1 h. The reaction was allowed to cool to room temperature, and 29 mL (21.05 g, 208.06 mmol) of triethylamine was added. The resulting white slurry was cooled to −50 °C, and an orange solution of tris(dibenzylideneacetone)dipalladium(0) chloroform complex (1.81 g, 1.75 mmol) and (3.63 g, 5.24 mmol) ligand L* = (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenyphosphinobenzoyl) in 25 mL of THF was slowly added. The orange reaction mixture was stirred mechanically at −50 °C for 1 h, stepwise warmed over a period of 5 h until 0 °C, and subsequently stirred overnight at room temperature. Solvent was removed under vacuum, and the crude product was purified by flash chromatography, eluting with 3:2 hexanes/EtOAc, to yield the desired product **6** (17.89 g, 92%) as a white solid (97% ee, as determined by chiral HPLC, Chiralcel OJ-column, 50:50 hexane/2-propanol, 1 mL/min, 210 and 245 nm, (−) 12.9 min, (+) 19.9 min). The enantiomeric excess was improved to >99% (11.13 g, 57% yield) by recrystallization from dichloromethane/hexanes. **6**: mp 119−122 °C (lit.[3] mp 121−125 °C); $[\alpha]^{20}_D$ = +141.27 (*c* = 0.865, CH_2Cl_2) (lit.[3] 99% ee, $[\alpha]^{20}_D$ = +114 (*c* = 2.52, CH_2Cl_2)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.69 (br d, *J* = 19 Hz, 1H), 2.81 (br dd, *J* = 19, 7 Hz, 1H), 5.11 (ddd, *J* = 7, 7, 1 Hz, 1H), 5.29 (br d, *J* = 7 Hz, 1H), 6.00 (br d, *J* = 7 Hz, 1H), 6.04 (br d *J* = 7 Hz, 1H), 7.35 (d, *J* = 8 Hz, 2H), 7.95 (d, *J* = 8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.7 (CH_3), 39.0 (CH_2), 66.3 (CH), 76.7 (CH), 128.0 (CH), 128.3 (CH), 129.7 (CH), 133.8 (CH), 135.0 (C_q), 145.5 (C_q), 151.3 (C_q); IR (neat, cm^{-1}) 3069, 2925, 2846, 1775, 1596, 1364, 1168, 1143; LRMS *m*/*z* 280 ([M − H]$^+$, <1), 215 (75), 170 (76), 91 (100); HRMS calcd for $C_{13}H_{14}NO_4S$ [M + H$^+$] 280.0644, found 280.0641. Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01. Found: C, 55,92; H, 4.78; N 5.16.

***N*-((1*S*,5*R*)-5-Hydroxycyclopent-2-enyl)-4-methylbenzenesulfonamide (7).** Oxazolidinone **6** (4.01 g, 14.35 mmol) and potassium hydroxide (2.42 g, 43.06 mmol) were suspended in 140 mL of methanol and the mixture heated to 70 °C for 2 h. Dichloromethane and saturated NaCl solution were added to the reaction mixture, the phases were separated, and the aqueous layer was extracted two times with dichloromethane. The dichloromethane phase was dried with magnesium sulfate, and the solvent was removed under vacuum. The desired product was purified by chromatography on silica gel using 1:1 hexanes/MTBE to yield **7** (3.55 g, 14.00 mmol, 98%) as a white solid. **7**: mp 59−61 °C; $[\alpha]^{20}_D$ = +13.27 (*c* = 0.985, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (br s, 1H), 2.33 (dddd, *J* = 18, 4, 2, 2 Hz, 1H), 2.44 (s, 3H), 2.57 (dddd, *J* = 18, 6, 4, 2 Hz, 1H), 4.22 (dddd, *J* = 6, 6, 4, 2 Hz, 1H), 4.25 (br d, *J* = 6 Hz, 1H), 5.22 (br d, *J* = 8 Hz, 1H), 5.35 (ddd, *J* = 6, 2, 2, Hz, 1H), 5.80 (ddd, *J* = 6, 4, 2 Hz, 1H), 7.32 (d, *J* = 8 Hz, 2H), 7.80 (d, *J* = 8 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ

21.5 (CH_3), 40.1 (CH_2), 61.4 (CH), 70.3 (CH), 127.2 (CH), 129.0 (CH), 129.8 (CH), 131.8 (CH), 137.3 (C_q), 143.6 (C_q); IR (neat, cm^{-1}) 3495, 3273, 3064, 2924, 1598, 1437, 1327, 1158; LRMS *m*/*z* 253 ([M^+], <1), 197 (19), 155 (21), 98 (100), 91 (80); HRMS calcd for $C_{12}H_{15}NO_3S$ [M^+] 253.0773, found 253.0778. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.78; H, 5.96; N, 5.68.

***N*-Allyl-*N*-((1*S*,5*R*)-5-hydroxycyclopent-2-enyl)-4-methylbenzenesulfonamide (8).** Amine **7** (9.65 g, 38.08 mmol), potassium carbonate (7.89 g, 57.12 mmol), and allyl bromide (4.8 mL, 6.86 g, 56.74 mmol) were suspended in 50 mL of DMF and the mixture stirred overnight at room temperature. Dichloromethane and a saturated NaCl solution were added to the suspension, and the aqueous layer was extracted two times with dichloromethane. The combined organic layers were dried with $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by a short column filtration on silica gel using 1:1 hexanes/MTBE to yield **8** (11.01 g, 37.53 mmol, 99%) as a white solid. **8**: mp 34−35 °C; $[\alpha]^{20}_D = +75.49$ ($c = 0.865$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (dddd, $J = 18$, 4, 4, 2 Hz, 1H), 2.43 (s, 3H), 2.65 (dddd, $J = 18$, 7, 3, 2 Hz, 1H), 3.71 (dddd, $J = 16$, 6, 2, 2 Hz, 1H), 4.01 (br dd, $J = 16$, 6 Hz, 1H), 4.47 (ddd, $J = 7$, 7, 4 Hz, 1H), 4. 61 (br d, $J = 7$ Hz, 1H), 5.11 (ddd, $J = 10$, 2, 2 Hz, 1H), 5.14 (ddd, $J = 18$, 2, 2 Hz, 1H), 5.39 (ddd, $J = 6$, 3, 2 Hz, 1H), 5.84 (dddd, $J = 18$, 10, 6, 6 Hz, 1H), 5.89 (ddd, $J = 6$, 4, 2 Hz, 1H), 7.31 (d, $J = 8$ Hz, 2H), 7.75 (d, $J = 8$ Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.5 (CH_3), 39.8 (CH_2), 48.6 (CH_2), 65.7 (CH), 70.7 (CH), 117.2 (CH_2), 126.8 (CH), 127.3 (CH), 129.7 (CH), 133.5 (CH), 135.8 (CH), 137.1 (C_q), 143.5 (C_q); IR (neat, cm^{-1}) 3525, 3065, 2925, 1640, 1598, 1332, 1157; LRMS *m*/*z* 293 ([M^+], 2), 237 (48), 155 (19), 138 (100), 91 (61); HRMS calcd for $C_{15}H_{19}NO_3S$ [M^+] 293.1086, found 293.1088. Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.38; H, 6.43; N, 4.93.

***N*-Allyl-*N*-[(1*S*,5*R*)-5-(*tert*-butyldimethylsilanyloxy)-cyclopent-2-enyl]-4-methylbenzenesulfonamide (9).** To a solution of the alcohol **8** (6.43 g, 21.91 mmol) and 2,6-lutidine (6.5 mL, 6.00 g, 55.99 mmol) in 20 mL of dichloromethane was added dropwise *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.5 mL, 6.37 g, 24.08 mmol). The reaction was stirred overnight at room temperature, concentrated in a vacuum, and purified by column chromatography on silica gel eluting with 8:2 hexanes/MTBE to yield the protected alcohol **9** (8.78 g, 21.53 mmol, 98%) as a colorless oil. **9**: $[\alpha]^{20}_D = +93.65$ ($c = 0.850$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 2.28 (dddd, $J = 18$, 4, 4, 2 Hz, 1H), 2.41 (s, 3H), 2.55 (dddd, $J = 18$, 7, 3, 2 Hz, 1H), 3.70 (dddd, $J = 16$, 6, 2, 2 Hz, 1H), 4.05 (br dd, $J = 16$, 6 Hz, 1H), 4.50 (ddd, $J = 7$, 7, 4 Hz, 1H), 4.78 (br d, $J = 7$ Hz, 1H), 4.96 (ddd, $J = 10$, 2, 2 Hz, 1H), 5.05 (ddd, $J = 18$, 2, 2 Hz, 1H), 5.43 (ddd, $J = 6$, 3, 2 Hz, 1H), 5.72 (dddd, $J = 18$, 10, 6, 6 Hz, 1H), 5.83 (ddd, $J = 6$, 4, 2 Hz, 1H), 7.25 (d, $J = 8$ Hz, 2H), 7.71 (d, $J = 8$ Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ −5.0 ($2CH_3$), −4.7 ($2CH_3$), 18.1 (C_q), 21.4 (CH_3), 25.9 (CH_3), 41.4 (CH_2), 49.1 (CH_2), 64.9 (CH), 72.0 (CH), 116.4 (CH_2), 127.1 (CH), 128.1 (CH), 129.4 (CH), 132.4 (CH), 136.3 (CH), 139.3 (C_q), 142.5 (C_q); IR (neat, cm^{-1}) 3064, 2928, 2856, 1640, 1599, 1342, 1160; LRMS *m*/*z* 392 ([$M^+ - CH_3$], 2), 350 (100), 268 (89), 252 (75), 73 (70); HRMS calcd for $C_{20}H_{30}NO_3SSi$ [$M^+ - CH_3$] 392.1716, found 392.1716. Anal. Calcd for $C_{21}H_{33}NO_3SSi$: C, 61.87; H, 8.16; N, 3.44. Found: C, 61.88; H, 7.96; N, 3.50.

(*S*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)but-3-enyl]-1-(toluene-4-sulfonyl)-2,5-dihydro-1*H*-pyrrole (10). The metathesis precursor **9** (6.02 g, 14.76 mmol) was dissolved in 300 mL of CH_2Cl_2, and 500 mL of C_2H_4 was slowly bubbled through the solution via a syringe. $Cl_2(PCy_3)_2RuCHPh$ (0.61 g, 0.74 mmol) was then added, and the mixture was stirred at 25 °C for 3 h. Subsequently, lead tetraacetate (0.49 g, 1.11 mmol) was added to the reaction mixture, and stirring was continued for an additional 14 h. The solvent was removed under vacuum, and the residue was then purified by column filtration over 0.30 g of silica gel using dichloromethane to yield dihydropyrrole **10** (5.90 g, 14.46 mmol, 98%) as a colorless solid. **10**: mp 77−79 °C; $[\alpha]^{20}_D = -205.22$ ($c = 0.938$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.15 (s, 3H), 0.86 (s, 9H), 2.24 (dddd, $J = 14$, 8, 2, 1 Hz, 1H), 2.30 (dddd, $J = 14$, 6, 2, 2 Hz, 1H), 2.41 (s, 3H), 4.03 (dddd, $J = 15$, 2, 2, 2 Hz, 1H), 4.10 (dddd, $J = 15$, 5, 2, 2 Hz, 1H), 4.22 (ddd, $J = 8$, 6, 2 Hz, 1H), 4.36 (m, 1H), 5.11 (ddd, $J = 10$, 2, 1 Hz, 1H), 5.12 (ddd, $J = 18$, 2, 2 Hz, 1H), 5.59 (dddd, $J = 6$, 2, 2, 2 Hz, 1H), 5.62 (dddd, $J = 6$, 2, 2, 1 Hz, 1H), 5.87 (dddd, $J = 18$, 10, 8, 6 Hz, 1H), 7.29 (d, $J = 8$ Hz, 2H), 7.65 (d, $J = 8$ Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ −4.6 (CH_3), −4.5 (CH_3), 18.0 (C_q), 21.5 (CH_3), 25.8 (CH_3), 40.2 (CH_2), 56.1 (CH_2), 71.2 (CH,), 74.1 (CH,), 117.3 (CH_2), 125.8 (CH), 125.9 (CH), 127.5 (CH), 129.7 (CH), 134.3 (C_q), 134.7 (CH), 143.4 (C_q); IR (neat, cm^{-1}) 2927, 2855, 1641, 1599, 1339, 1160; LRMS *m*/*z* 392 ([$M^+ - CH_3$], 3), 350 (89), 222 (29), 213 (17), 185 (100), 91 (29), 73 (93); HRMS calcd for $C_{20}H_{30}NO_3SSi$ [$M^+ - CH_3$] 392.1716, found 392.1716. Anal. Calcd for $C_{21}H_{33}NO_3SSi$: C, 61.87; H, 8.16; N, 3.44. Found: C, 61.97; H 8.05; N, 3.66.

(*R*)-4-(*tert*-Butyldimethylsilanyloxy)-4-[(*S*)-1-(toluene-4-sulfonyl)-2,5-dihydro-1*H*-pyrrol-2-yl]butan-1-ol (11). Alkene **10** (2.53 g, 6.21 mmol) was dissolved in 130 mL of THF and cooled to 0 °C, and a 0.5 M solution of 9-BBN-H (14 mL, 7.00 mmol) was slowly added. The reaction mixture was allowed to warm to room temperature and then heated to 55 °C, and stirring was continued for 8 h. Two hundred milliliters of ethanol, 12 mL of a 6 M solution of sodium hydroxide, and 7 mL of a 30% hydrogen peroxide solution were then added, and the solution was refluxed for 1 h. The solvent was concentrated, MTBE and saturated NaCl solution were added, and the aqueous layer was extracted three times with MTBE. The combined organic layers were dried with $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel eluting with 3:2−1:1 hexanes/MTBE to yield the alcohol **11** (2.19 g, 5.15 mmol, 83%) as a colorless solid. **11**: mp 79−81 °C; $[\alpha]^{20}_D = -208.02$ ($c = 0.935$, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) δ 0.28 (s, 3H), 0.46 (s, 3H), 1.08 (s, 9H), 1.51−1.79 (m, 4H), 1.93 (s, 3H), 3.48 (m, 2H), 4.06 (dddd, $J = 15$, 2, 2, 2 Hz, 1H), 4.15 (dddd, $J = 15$, 5, 2, 2 Hz, 1H), 4.46 (ddd, $J = 7$, 7, 2 Hz, 1H), 4.52 (dddd, $J = 5$, 2, 2, 1 Hz, 1H), 5.17 (dddd, $J = 6$, 2, 2, 1 Hz, 1H), 5.37 (dddd, $J = 6$, 2, 2, 1 Hz, 1H), 6.85 (d, $J = 8$ Hz, 2H), 7.80 (2d, $J = 8$ Hz, 2H); ^{13}C NMR (125.8 MHz, C_6D_6) δ −4.3 (CH_3), −4.1 (CH_3), 18.3 (C_q), 21.0 (CH_3), 26.2 (CH_3), 29.4 (CH_2), 32.1 (CH_2), 56.4 (CH_2), 62.5 (CH_2), 71.9 (CH), 75.1 (CH), 125.9 (CH), 126.4 (CH), 127.9 (CH), 129.7 (CH), 135.4 (C_q), 143.1 (C_q); IR (neat, cm^{-1}) 3526, 3417, 2928, 2856, 1598, 1344, 1162; LRMS *m*/*z* 426 ([MH^+], <1), 368 (19), 222 (34), 203 (23), 155 (25), 91 (50), 71 (100), 69 (79), 55 (32); HRMS calcd for $C_{21}H_{36}NO_4SSi$ [MH^+] 426.2134, found 426.2139. Anal. Calcd for $C_{21}H_{35}NO_4SSi$: C, 59.26; H, 8.29; N, 3.29. Found: C, 59.19; H 8.16; N, 3.41.

(*S*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-4-hydroxybutyl]-2,5-dihydropyrrole-1-carboxylic Acid Allyl Ester (12). Alcohol **11** (3.17 g, 7.44 mmol) and $K_2HPO_4 \cdot 3H_2O$ (12.08 g, 52.93 mmol) were dissolved in 160 mL of MeOH. Na/Hg (136 g, freshly prepared from 145 g of Hg and 5.3 g of Na) was added, and the mixture was refluxed for 2 h. The solution was decanted, H_2O was then added, and the aqueous layer was extracted four times with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, and solvent was removed under vacuum. The crude product was then dissolved in 140 mL of CH_2Cl_2/H_2O (1:1), and with vigorous stirring NaOH (1.80 g, 44.90 mmol) and allyl chloroformate (1.0 mL, 1.17 g, 9.70 mmol) were added. After 1 h, phases were separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was chromatographed on silica gel using 3:2 hexanes/EtOAc to give **12** (2.35 g, 6.62 mmol, 89%) as a colorless oil. **12**: $[\alpha]^{20}_D = -184.75$ ($c = 0.885$, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) two rotamers (ratio: 3:1) δ 0.16 (s, 3H), 0.17 (s, 3H), 1.03 (s, 9H), 1.50−1.80 (m, 4H), 3.48 (br s, 0.5H), 3.56−3.61 (m, 1.5H), 4.01−4.12 (m, 1.5H), 4.18 (br dd, $J = 16$, 6 Hz, 0.25H), 4.28 (br t, $J = 6$ Hz, 0.25H), 4.40 (br d, $J = 16$ Hz, 0.25H), 4.49 (br s, 0.25H), 4.57 (br t, $J = 6$ Hz, 0.75H), 4.65 (br dd, $J = 13$, 6 Hz, 1H), 4.69−4.78 (m, 1.75H), 5.11 (br d, $J = 10$ Hz, 1H), 5.26 (br d, $J = 17$ Hz, 0.25H), 5.28 (br d, $J = 18$

Hz, 0.75H), 5.45 (br dddd, J = 6, 2, 2, 1 Hz, 0.75H), 5.51 (br d, J = 6 Hz, 0.25H), 5.58 (br d, J = 6 Hz, 0.25H), 5.64 (br dddd, J = 6, 2, 2, 1 Hz, 0.75H), 5.94 (dddd, J = 17, 10, 6, 5 Hz, 1H); ^{13}C NMR (125.8 MHz, C_6D_6) δ −4.9, −4.7 (CH_3), −4.4, −4.3 (CH_3), 18.2 (C_q), 26.0 (CH_3), 29.5 (CH_2), 32.0 (CH_2), 54.1, 55.0 (CH_2), 62.4 (CH_2), 65.7, 65.8 (CH_2), 68.7, 69.5 (CH), 71.2, 72.5 (CH), 117.1, 117.3 (CH_2), 125.84, 126.1 (CH), 126.4, 126.8 (CH), 133.7, 134.3 (CH), 154.5 (C_q); IR (neat, cm^{-1}) 3434, 2929, 2857, 1707, 1687, 1627; LRMS m/z 356 ([MH$^+$], <1), 298 (18), 240 (6), 152 (32), 73 (62), 71 (100); HRMS calcd for $C_{18}H_{34}NO_4Si$ [MH$^+$] 356.2257, found 356.2254. Anal. Calcd for $C_{18}H_{33}NO_4Si$: C, 60.81; H, 9.36; N, 3.94. Found: C, 60.56; H 9.18; N, 4.15.

(*S*)-2-[(*R*)-1-(*tert*-Butyldimethylsilanyloxy)-4-methanesulfonyloxybutyl]-2,5-dihydropyrrole-1-carboxylic Acid Allyl Ester (13). Alcohol **12** (0.80 g, 2.26 mmol) and triethylamine (0.95 mL, 0.69 g, 6.83 mmol) were dissolved in 40 mL of CH_2Cl_2 and cooled to 0 °C. Subsequently, methanesulfonyl chloride (0.21 mL, 0.31 g, 2.71 mmol) was added dropwise, and the solution was allowed to warm to rt. After 2 h of stirring at rt, saturated $NaHCO_3$ solution was added, and the aqueous phase was extracted three times with dichloromethane. The organic phases were dried with Na_2SO_4 and concentrated. The residue was chromatographed on silica gel using 3:2 hexanes/EtOAc to give **13** (0.96 g, 2.21 mmol, 98%) as a colorless oil. **13**: $[\alpha]^{20}_D$ = −154.25 (c = 0.870, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) two rotamers (ratio: 3:1) δ 0.11 (br s, 3H), 0.13 (br s, 3H), 1.00 (br s, 9H), 1.34−1.56 (m, 3H), 1.61−1.75 (m, 1H), 2.27 (br s, 0.75H), 2.33 (br s, 2.25H), 3.89 (br s, 0.50H), 3.94 (t, J = 6 Hz, 1.50H), 3.98−4.20 (m, 2H), 4.33−4.41 (m, 0.5H), 4.45 (br t, J = 6 Hz, 0.75H), 4.55 (br s, 0.75H), 4.63 (dd, J = 14, 6 Hz, 0.75H), 4.67−4.78 (m, 1.25H), 5.10 (br d, J = 10 Hz, 0.75H), 5.11 (br d, J = 10 Hz, 0.25H), 5.25 (br d, J = 17 Hz, 0.25H), 5.26 (br d, J = 17 Hz, 0.75H), 5.41−5.55 (m, 2H), 5.93 (dddd, J = 17, 10, 6, 6 Hz, 1H); ^{13}C NMR (125.8 MHz, C_6D_6) δ −4.9, −4.7 (CH_3), −4.4, −4.4 (CH_3), 18.1 (C_q), 26.0 (CH_2), 26.0 (CH_3), 31.3 (CH_2), 36.6 (CH_3), 54.1, 55.0 (CH_2), 65.6, 65.9 (CH_2), 68.9, 69.3 (CH_2), 68.6, 69.4 (CH), 70.7, 72.0 (CH), 117.1, 117.7 (CH_2), 125.6, 126.1 (CH), 126.4, 127.1 (CH), 128.5, 133.7 (CH), 154.5, 160.5 (C_q); IR (neat, cm^{-1}) 2929, 2857, 1703, 1628, 1408, 1358, 1176; LRMS m/z 418 ([M$^+$ − CH_3], 2), 376 (38), 281 (49), 185 (23), 153 (50), 71 (100); HRMS calcd for $C_{18}H_{32}NO_6SSi$ [M$^+$ − CH_3] 418.1720, found 418.1720. Anal. Calcd for $C_{19}H_{35}NO_6SSi$: C, 52.63; H, 8.14; N, 3.23. Found: C, 52.42; H 8.09; N, 3.28.

(8*R*,8a*S*)-8-(*tert*-Butyldimethylsilanyloxy)-3,5,6,7,8,8a-hexahydroindolizine (14). To a mixture of polymer-bound Pd(0) catalyst (freshly prepared from palladium acetate (0.05 g, 0.23 mmol) and polymer-bound triphenylphosphine (0.77 g, 2.31 mmol) in 25 mL of THF, shaken for 1 h at room temperature) was added a solution of **13** (1.00 g, 2.31 mmol) in 55 mL of THF, triethylamine (3 mL, 40.78 mmol) and dimedone (2.26 g, 16.14 mmol). The mixture was shaken for 3 h at room temperature and subsequently for 3 h at 50 °C. The suspension was then chromatographed over basic aluminum oxide using THF as eluent to yield the desired indolizidine **14** (0.56 g, 2.19 mmol, 95%) as a slightly yellow oil. **14**: $[\alpha]^{20}_D$ = −91.73 (c = 0.955, C_6H_6); ^{1}H NMR (500 MHz, C_6D_6) δ 0.13 (s, 3H), 0.15 (s, 3H), 1.07 (s, 9H), 1.36 (dddd, J = 13, 13, 10, 4 Hz, 1H), 1.46−1.53 (m, 1H), 1.62−1.74 (m, 1H), 1.97 (br dddd, J = 13, 4, 4, 4 Hz, 1H), 2.32 (ddd, J = 12, 12, 6 Hz, 1H), 2.81 (br dd, J = 12, 5 Hz, 1H), 3.09−3.15 (m, 1H), 3.21 (dddd, J = 12, 6, 2, 1 Hz, 1H), 3.62 (dddd, J = 12, 4, 2, 2 Hz, 1H), 3.68 (ddd, J = 10, 9, 4 Hz, 1H), 5.77 (dddd, J = 6, 2, 2, 2 Hz, 1H), 6.26 (br d, J = 6, Hz, 1H); ^{13}C NMR (125.8 MHz, C_6D_6) δ −4.5 (CH_3), −4.1 (CH_3), 18.2 (C_q), 25.1 (CH_2), 26.0 (CH_3), 35.0 (CH_2), 49.0 (CH_2), 58.3 (CH_2), 72.5 (CH), 74.8 (CH), 128.8 (CH), 131.4 (CH); IR (neat, cm^{-1}) 2929, 2856, 2778, 1616; LRMS m/z 253 ([M$^+$], <1), 196 (100), 154 (22), 120 (30), 75 (12); HRMS calcd for $C_{14}H_{27}NOSSi$ [M$^+$] 253.1862, found 253.1866. Anal. Calcd for $C_{19}H_{35}NOSSi$: C, 66.34; H, 10.74; N, 5.53. Found: C, 65.97; H 10.77; N, 5.18.

Acetic Acid (1*S*,2*R*,8*R*,8a*R*)-1,2-Diacetoxyoctahydroindolizin-8-yl Ester (15). AD-mix-α (4.29 g) and methanesulfonamide (0.18 g, 1.85 mmol) were dissolved in 15 mL of a 1:1 solution of *tert*-butyl alcohol and water. The mixture was stirred at room temperature until both phases were clear and then cooled to 0 °C, whereupon the inorganic salts partially precipitated. The olefin **14** (0.42 g, 1.64 mmol) was added at once, and the heterogeneous slurry was stirred vigorously at 3−6 °C for 1 week. The reaction was quenched by addition of 50 mL of a saturated sodium sulfite solution and stirred for 60 min. The reaction mixture was extracted several times with ethyl acetate, dried with Na_2SO_4, and concentrated. The residue was passed through a short pad of silica gel using 10:1 CH_2Cl_2/MeOH to give a mixture of crude dihydroxylated products. To a solution of the crude alcohols in 6.5 mL of THF was added TBAF (4 mL of a 1.0 M solution in THF), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated, CH_2Cl_2 (6.5 mL), pyridine (1.2 mL, 14.91 mmol), DMAP (40 mg, 0.33 mmol), and acetic anhydride (0.9 mL, 9.52 mmol) were added, and stirring was continued overnight at room temperature. The reaction mixture was then quenched with MeOH and concentrated to dryness. Column chromatography on silica gel using 1:1 hexanes/EtOAc afforded a 20:1 mixture of **15**/**16** (334 mg, 1.12 mmol, 68%) as a yellow oil. The diastereomers were then separated by chromatography using 2:1 hexanes/EtOAc as eluent, to give **15** (291 mg) and **16** (15 mg). Compound **15**: $[\alpha]^{20}_D$ = +7.04 (c = 0.895, MeOH) (lit.[13] $[\alpha]^{20}_D$ = +7.0 (c = 1.77, MeOH)); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18−1.28 (m, 1H), 1.70−1.79 (m, 2H), 1.91 (ddd, J = 11, 11, 4 Hz, 1H), 1.99 (s, 3H), 2.05 (s, 3H), 2.09 (s, 3H), 2.11−2.17 (m, 2H), 2.58 (dd, J = 11, 8 Hz, 1H), 3.05 (ddd, J = 10, 3, 3 Hz, 1H,), 3.16 (br d, J = 11 Hz, 1H), 4.95 (ddd, J = 11, 10, 5 Hz, 1H), 5.21 (ddd, J = 8, 6, 2 Hz, 1H), 5.52 (dd, J = 6, 4 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 20.5 (CH_3), 20.6 (CH_3), 21.0 (CH_3), 23.3 (CH_2), 29.8 (CH_2), 51.8 (CH_2), 59.3 (CH_2), 68.1 (CH), 69.2 (CH), 69.8 (CH), 70.2 (CH), 170.0 (C_q), 170.0 (C_q), 170.2 (C_q); IR (neat, cm^{-1}) 2945, 2801, 1738, 1254, 1237; LRMS m/z 300 ([MH$^+$], 2), 239 (21), 180 (12), 137 (29), 120 (100); HRMS calcd for $C_{14}H_{21}NO_6$ [MH$^+$] 300.1447, found 300.1451. Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.07; H 7.13; N, 4.50.

(1*S*,2*R*,8*R*,8a*R*)-Octahydroindolizine-1,2,8-triol [(−)-Swainsonine] (1). To a solution of trisacetate **15** (54.6 mg, 0.182 mmol) in 3 mL of methanol was added Amberlite resin (50 mg, Amberlite IRA-401(OH)). The reaction mixture was shaken for 2 h and filtered through a frit, and the resin was rinsed with methanol. After the filtrate was concentrated, (−)-swainsonine **1** (30.6 mg, 0.177 mmol, 96%) was obtained as colorless crystals. NMR spectroscopy indicated complete conversion, and no further purification was required. **1**: mp 143−145 °C (lit.[13] mp 144−145 °C); $[\alpha]^{20}_D$ = −89.74 (c = 0.575, MeOH) (lit.[13] $[\alpha]^{20}_D$ = −87.2 (c = 2.1, MeOH)); ^{1}H NMR (500 MHz, D_2O) δ 1.04−1.13 (m, 1H), 1.31−1.42 (m, 1H), 1.53−1.60 (m, 1H), 1.76 (dd, J = 10, 4 Hz, 1H), 1.80 (ddd, J = 12, 11, 4 Hz, 1H), 1.91 (dddd, J = 12, 3, 3, 3 Hz, 1H), 2.40 (dd, J = 11, 8 Hz, 1H), 2.71−2.78 (m, 2H), 3.65 (ddd, J = 11, 10, 5 Hz, 1H), 4.10 (dd, J = 6, 4 Hz, 1H), 4.20 (ddd, J = 7, 6, 3 Hz, 1H); ^{13}C NMR (125.8 MHz, D_2O, ref MeOH, 49.00) δ 22.9 (CH_2), 32.2 (CH_2), 51.4 (CH_2), 60.3 (CH_2), 66.1 (CH), 68.8 (CH), 69.4 (CH), 72.5 (CH); IR (neat, cm^{-1}) 3368, 2942, 2801, 2726, 1347, 1127, 1073; LRMS m/z 173 ([M$^+$], 25), 155 (25), 138 (16), 113 (100), 96 (89); HRMS calcd for $C_8H_{15}NO_3$ [M$^+$] 173.1052, found 173.1046. Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.30; H 8.72; N 7.84.

Acknowledgment. This work was supported by the Graduiertenkolleg Synthetische, mechanistische und reaktionstechnische Aspekte von Metallkatalysatoren and by the Fond der Chemischen Industrie.

Supporting Information Available: Proton and carbon NMR spectra are available for compounds **6**−**15** and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025589U

(13) Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29−32.