An Enantioselective Route to *cis*- and *trans*-2-(Hydroxymethyl)-5-alkylpyrrolidines

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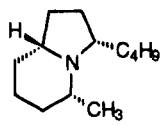
A general method for the enantioselective preparation of 2,5-disubstituted pyrrolidines has been developed. A variety of *cis*- and *trans*-2-(hydroxymethyl)-5-alkylpyrrolidines were synthesized using 1-(benzyloxy)-5-(*p*-toluenesulfonamido)-3-alken-2-ols as common intermediates.

Introduction

In relation to an ongoing project to synthesize monomorine (**1**), the need for an efficient method to prepare 2-(hydroxymethyl)-5-alkylpyrrolidines (**2**) in enantiomerically pure form has arisen. In addition to the present need, 2,5-disubstituted pyrrolidines have found extensive use in synthetic organic chemistry. Compounds with this basic structure have been used as auxiliaries in asymmetric synthesis[1,2] and as building blocks in natural product synthesis. A variety of pyrrolidine,[3] pyrrolizidine,[4] and indolizidine alkaloids[5] are readily accessible from 2-(hydroxymethyl)-5-alkylpyrrolidines *cis*- and *trans*-**2**. For example (−)-xenovenine (**3**), isolated from the cryptic thief ants Solenopsis and Monomorium,[4b] has been synthesized by Momose et al. utilizing a 2-(hydroxymethyl)-5-alkylpyrrolidine as a stereodefined key intermediate. It is therefore desirable to find methods for the stereoselective preparation of these types of compounds.[3-6]



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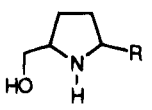

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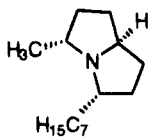

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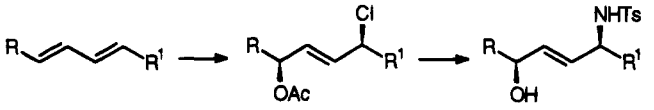
The utility of 4-amido-2-alken-1-ols (**6**, Scheme 1) as intermediates in the synthesis of natural products of the alkaloid group has been demonstrated previously. For example, various pyrrolidine[7] and tropa alkaloids[8,9] have been prepared using **6** and related cyclic precursors as key intermediates. Using the approach depicted in Scheme 1, preparation of the required amidoalkenols is achieved by palladium(II)-catalyzed 1,4-acetoxychlorination[10] of conjugated dienes **4** followed by palladium(0)-catalyzed nucleophilic substitution using the sodium salt of tosylamide.[11]

Scheme 1



4 **5** **6**

Although viable, this route suffers from two drawbacks: (i) it is not enantioselective, and (ii) when $R \neq R^1$ a mixture of regioisomeric products is obtained. In addition to the route in Scheme 1, several other approaches to 4-amino-2-alken-1-ol derivatives have been described previously;[12] however, none of these methods is completely general. In order to extend the flexibility of intermediates of type **6** we have developed a new and general method for their enantioselective preparation which also allows for further functionalization. Described herein is the preparation of these intermediates, as well as their use in the synthesis of 2-(hydroxymethyl)-5-alkylpyrrolidines.

Results and Discussion

In order to demonstrate the viability of this route as an enantioselective method for preparation of the title compounds, *cis*-2-(hydroxymethyl)-5-methylpyrrolidine (**7**) and *trans*-*N*-(*p*-toluenesulfonamido)-2-(hydroxymethyl)-5-butylpyrrolidine (**8**) have been synthesized in their enantiomerically pure form starting from (2*R*,3*S*)-4-(benzyloxy)-2,3-epoxybutan-1-ol (**9**) and (2*S*,3*S*)-4-(benz-

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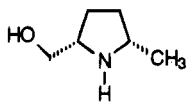
Table 1. Wittig Olefination and Epoxide Opening

	vinyl epoxide **11**			vinyl epoxide **15**		
R	yield (%)	(*Z*:*E*)[a]	amidoalkenol **12** (syn) yield (%)	yield (%)	(*Z*:*E*)[b]	amidoalkenol **16** (anti) yield (%)
a CH_3	61	(89:11)	86	60	(89:11)	89
b n-C_3H_7	54	(95:5)	67	70	(95:5)	81
c n-C_4H_9	77	(95:5)	68	78	(92:8)	91

[a] *E*:*Z* ratio was determined by NMR and the isomers were separated by HPLC using 95:5 hexane:EtOAc. [b] *E*:*Z* ratio was determined by NMR; the isomers were not seperated.[18]

yloxy)-2,3-epoxybutan-1-ol (**13**), respectively. All other compounds described herein were prepared in their racemic form.



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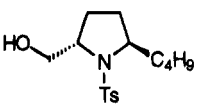

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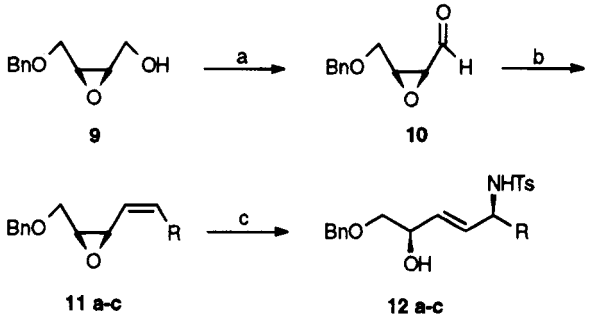
Epoxy alcohol **9** can be obtained in enantiomerically pure form from (*Z*)-butene-1,4-diol via monobenzylation followed by Sharpless epoxidation[13] and is also commercially available in both of its enantiomeric forms as the corresponding *p*-nitrobenzoate ester.[14] Careful tetrapropylammonium perruthenate (TPAP) oxidation[15] of epoxide **9** gave the moderately stable aldehyde **10** in 76% yield. Subsequent Wittig olefination[16] afforded vinyl epoxides **11a–c** (Scheme 2, Table 1). The *Z*:*E* selectivity

Scheme 2[a]

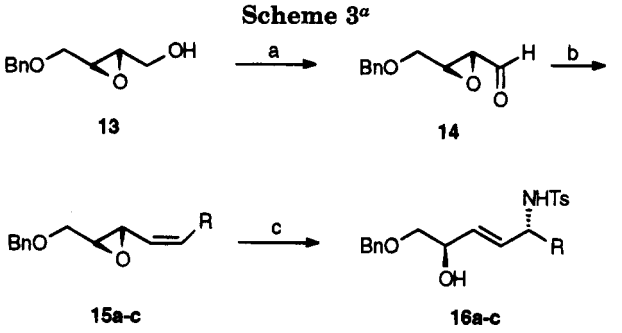


[a] Key (a) TPAP, NMO, CH_2Cl_2, mol sieves 4 Å; (b) $RCH_2(PPh_3)Br$, KOtBu; (c) NH_2Ts, NaNHTs, $Pd(PPh_3)_4$, CH_3CN.

in the Wittig reactions ranged from 89:11 to 95:5 and increased with increasing alkyl chain length (Table 1).

Palladium(0)-catalyzed nucleophilic opening of vinyl epoxides[12a,17] **11a–c** by NaNHTs/NH_2Ts[11] in CH_3CN at 40 °C gave *syn*-amidoalkenols **12a–c** with high stereo- and regioselectivity. None of the corresponding 1,2 adduct was obtained, and no epimerization at C_5 was observed. The corresponding *anti*-amidoalkenols **16a–c** (Scheme 3) were obtained from *trans*-epoxy alcohol[13] **13** via an analogous route. The yields and *Z*:*E* selectivities

Scheme 3[a]



[a] Key (a) TPAP, NMO, CH_2Cl_2, mol sieves 4 Å; (b) $RCH_2(PPh_3)Br$, KOtBu; (c) NH_2Ts, NaNHTs, $Pd(PPh_3)_4$, CH_3CN.

were in the same range as for the reaction sequence starting with epoxide **9** (Table 1).

Synthesis of 2-(Hydroxymethyl)-5-alkylpyrrolidines. Olefin **12a** was hydrogenated quantitatively to compound **17a** using 5% of Adams' catalyst in EtOH under 1 atm of hydrogen pressure for 20 min (Scheme 4).[19] Careful monitoring of this reaction is necessary to avoid debenzylation of the protected hydroxymethyl, which begins to occur after *ca.* 20 min. Mesylation followed by K_2CO_3-promoted cyclization[7] afforded pyrrolidine **19a** in 90% yield from **17a**.

Initially, detosylation was attempted using sodium naphthalide; however, under these conditions side products arising from radical induced ring opening were observed. Detosylation was ultimately accomplished with Na(Hg) in phosphate-buffered MeOH[20] to give **20** in 81% yield. Finally, (2*S*,5S)-2-(hydroxymethyl)-5-methylpyrrolidine (**7**) was obtained in 92% yield with an $[\alpha]^{25}_D$ +8.8° (*c* 0.4, EtOH)[21] by removal of the benzyl protective group via Pd/C-catalyzed hydrogenation in acidic MeOH.[9] The enantiomeric purity of **7** was determined to be >96% ee by examination of the ^1H NMR using mandelic acid as a chiral shift reagent.[22] The *trans*-*N*-(*p*-toluenesulfonamido)-2-[(benzyloxy)methyl]-5-methylpyrrolidine (**23a**) was accessible from **16a** by the

(13) (a) Epoxy alcohols **9** (Scheme 2) and **13** (Scheme 3) have been prepared in both enantiomeric forms via asymmetric epoxidation of the corresponding olefins[13b,c] or from D- and L-tartaric acid.[d] (b) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D. Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. (c) Pfenniger, A. Synthesis **1986**, 89. (d) Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 687.

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(18) While the *E* and *Z* isomers of the *cis*-vinyl epoxide are, with difficulty, able to be separated by HPLC, the corresponding isomers from the *trans*-vinyl epoxides are not readily separated. Specifically, it is possible to separate small amounts of the *Z* isomer by careful cutting and recycling of HPLC fractions (98:2 hexane:EtOAc). In practice, however, this was found to be unnecessary in all examples except those where R = Me. In cases where the *E*:*Z* selectivity was high (i.e., all cases except where R = Me) the minor isomer is lost after the next two reactions (i.e., nucleophilic epoxide opening and double bond reduction). This is most certainly due to small differences in the reactivity and the R_f of the two diatereomers.

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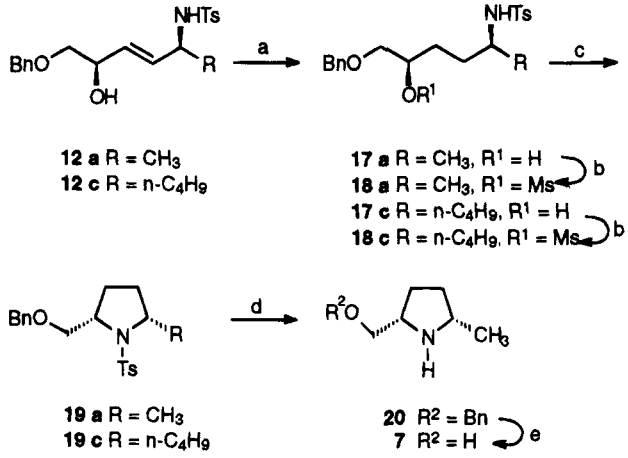
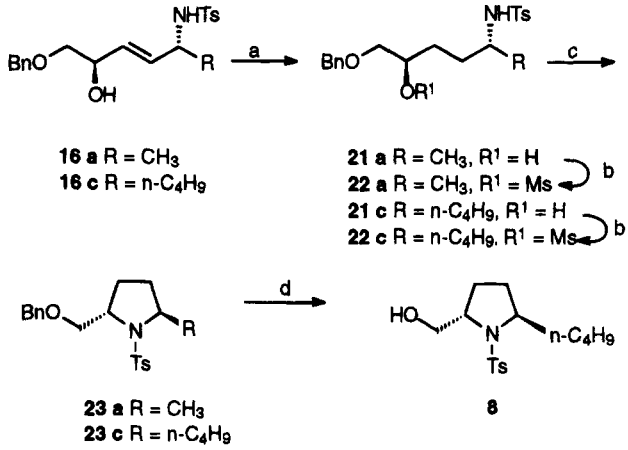
(21) Lhommet et al. (ref 4c) have reported an optical rotation of 1 of $[\alpha]^{25}_D$ +2° (*c* 1.91, EtOH) for the corresponding (2*S*,5*R*) isomer.

Scheme 4[a]



[a] Key (a) PtO_2, EtOH; (b) MsCl, Et_3N, THF; (c) K_2CO_3, MeOH; (d) Na(Hg), Na_2HPO_4, MeOH; (e) Pd/C, $MeSO_3H$, MeOH.

Scheme 5[a]



[a] Key (a) PtO_2, H_2, EtOH; (b) MsCl, Et_3N, THF; (c) K_2CO_3, MeOH; (d) Pd/C, H_2, MeOH.

analogous route outlined in Scheme 5. Furthermore, pyrrolidine **23c** was debenzylated by hydrogenation with Pd/C in MeOH to give *trans*-*N*-(*p*-toluenesulfonamido)-2-(hydroxymethyl)-5-butylpyrrolidine (**8**) in 95% yield with >98% ee[23] and an $[\alpha]^{25}_D$ −22.6° (*c* 1.09, $CHCl_3$).

Conclusion

Detailed herein is a straightforward method for the synthesis of 2-(hydroxymethyl)-5-alkylpyrrolidines. Preparation of the title compounds utilizes an approach based on the use of 4-amido-2-alken-1-ols as key intermediates. The versatility of this method hinges on the ease of preparation of a wide variety of these amidoalkenol intermediates with complete control of both absolute and relative stereochemistry. Since 2-(hydroxymethyl)-5-alkylpyrrolidines serve as useful building blocks in alkaloid synthesis, the enantioselective synthesis of these compounds represents an important contribution to the total synthesis of both natural and unnatural alkaloids.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded on a Varian XL 300 spectrometer or a Varian Unity 400 spectrometer. Coupling constants (*J*) are given in Hz, and the following abbreviations are used: apparent (app), broad (br), exchangable (exch). IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer and were examined as thin films on NaBr plates unless otherwise stated. Optical rotations were measured using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Analytische Laboratorien, Grummersbach, Germany.

Thin-layer chromatography was performed with E. Merck silica gel 60F-254 precoated aluminum sheets of 0.2-mm thickness which were visualized with appropriate combinations of UV light and phosphomolybdic acid stain (10% phosphomolybdic acid in ethanol). Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). THF and Et_2O were distilled from a deep blue ketyl immediately before use. CH_2Cl_2 was distilled from CaH, and CH_3CN was dried over 4Å molecular sieves prior to use. All other solvents were reagent grade quality and used as received. Tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$),[10b,24] tetrapropylammonium perruthenate (TPAP, RuO_4NPr_4),[25] and the sodium salt of tosylamide (NaNHTs)[26] were prepared according to literature procedures. Na_2SO_4 was used as the drying agent in all workup procedures. All reactions were run in flame-dried glassware under nitrogen atmosphere unless stated otherwise. Product purity was determined by NMR and/or HPLC.

(2*R*,3*S*)-4-(Benzyloxy)-2,3-epoxybutan-1-ol (9). Racemic **9** is readily available from the corresponding *cis*-2-butene-1,4-diol via monobenzylation (1 equiv NaH, BnBr, THF) followed by epoxidation (*m*-CPBA, CH_2Cl_2).[9] All spectral data for this compound were in accordance with literature values.[13] Enantiomerically pure **9** was obtained from the commercially available (2*R*,3*S*)-4-(benzyloxy)-2,3-epoxybutan-1-ol *p*-nitrobenzoate ester. Hydrolysis of the nitrobenzoate ester with 1% NaOH in MeOH gave the desired epoxy alcohol **9** in 90% yield.

***trans*-2-Butene-1,4-diol.** *trans*-2-Butene-1,4-diol was synthesized according to literature procedure[27] from 2-butyne-1,4-diol via reduction with $LiAlH_4$. All spectral data were in accordance with literature values.

(2*S*,3*S*)-4-(Benzyloxy)-2,3-epoxybutan-1-ol (13). Racemic **13** was prepared from the corresponding *trans*-2-butene-1,4-diol via monobenzylation and epoxidation, as above. The spectral data for **13** were in accordance with literature values.[13] Enantiomerically pure **13** was prepared in the following manner: Sharpless asymmetric epoxidation of the corresponding (benzyloxy)butenol gave **13** with 87% ee.[13] This mixture was enriched by formation of the crystalline 2,5-dichlorobenzoate derivative (2,5-dichlorobenzoyl chloride, diisopropylethylamine, CH_2Cl_2, 0 °C, 96%) followed by recrystallization from cyclohexane/hexane (ca. four times). Finally, cleavage of the benzoate ester was accomplished with 1% NaOH in MeOH to give **13** in 97% yield with >98% ee:[22] $[\alpha]^{25}_D$ −22.8° (*c* 1.55, $CHCl_3$).

(2*S*,3*S*)-4-(Benzyloxy)-2,3-epoxybutanal (10). *N*-Methylmorpholine *N*-oxide (5.97 g, 50.9 mmol) and activated crushed 4 Å molecular sieves (1.78 g) were suspended in 250 mL of CH_2Cl_2. (2*R*,3*S*)-4-(Benzyloxy)-2,3-epoxybutan-1-ol (6.40 g, 33 mmol) was added as a solution in 20 mL of CH_2Cl_2. The mixture was cooled to 0 °C, and TPAP (337 mg, 0.96 mmol) was added in portions. The reaction was stirred at rt for 3.5 h, after which the mixture was introduced onto a silica column

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(23) The enantiomeric purity of alcohols **8** (Scheme 5) and **13** (Scheme 3) was determined by analysis of the ^{31}P NMR spectum of the corresponding phosponates. Both were found to have >98% ee. Welch, C. J. *Tetrahedron Asymmetry* **1991**, *2*, 1127. Feringa, B. L.; Smaardijk, A.; Wynberg, H. *J. Am. Chem. Soc.* **1985**, *107*, 4798.

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and the silica was eluted with 150 mL of CH_2Cl_2. After concentration of the CH_2Cl_2 eluant 4.81 g (76%) of a pale yellow oil was collected: ^{1}H NMR δ 9.43 (d, J = 3.2, 1 H), 7.32 (m, 5 H), 4.58 (s, 2 H), 3.82 (dd, J = 8.2, 3.2, 1 H), 3.80 (dd, J = 8.2, 2.2, 1 H), 3.50 (dt, J = 3.2, 2.2, 1 H), 3.43 (t, J = 3.2, 1 H); ^{13}C NMR δ 197.2, 137.0, 128.5, 128.0, 127.8, 73.6, 66.2, 58.0, 57.3; IR 3425, 3064, 3031, 2863, 2359, 1724, 1496, 1453, 1094, 739, 700 cm^{-1}; $[\alpha]^{25}_D$ −108° (c 1.1, $CHCl_3$).

(4*Z*)-(2*S*,3*R*)-1-(Benzyloxy)-2,3-epoxy-4-hexene (11a). *t*-BuOK (701 mg, 6.2 mmol) was dissolved in 50 mL of THF and the solution cooled to −78 °C. $C_2H_5(PPh_3)Br$ (2.3 g, 6.2 mmol) was added, and the resulting yellow mixture was stirred for 20 min. A solution of compound **9** (1 g, 5.2 mmol) in 10 mL of THF was added dropwise, and the reaction was stirred at −78 °C for 1.5 h. After being stirred for an additional hour at rt, the reaction mixture was partitioned between ether and brine. Drying and concentration of the organic layer afforded a pale yellow oil in 86% yield (914 mg). The *Z*:*E* ratio was determined to be 89:11. The isomers were separated by HPLC (SiO_2, pentane/ether 95/5): ^{1}H NMR δ 7.3 (m, 5 H), 5.86 (dq, J = 11.1, 7.0, 1 H), 5.20 (ddq, J = 11.1, 8.0, 1.8, 1 H), 4.79 (d, J = 12.0, 1 H), 4.68 (d, J = 12.0, 1 H), 3.74 (dd, J = 8.0, 4.0, 1 H), 3.70 (dd, J = 11.1, 4.0, 1 H), 3.56 (dd, J = 6.4, 11.1, 1 H), 3.38 (ddd, J = 6.4, 4.0, 4.0, 1 H), 1.78 (dd, J = 7.0, 1.8, 3 H); ^{13}C NMR δ 137.9, 132.3, 128.4, 127.8, 127.7, 123.8, 73.3, 68.5, 56.7, 51.7, 13.5; IR 3031, 2919, 2858, 1746, 1652, 1496, 1095, 1028 cm^{-1}; $[\alpha]^{25}_D$ −67.9° (c 1.1, $CHCl_3$).

(4*Z*)-(2*S,3*R**)-1-(Benzyloxy)-2,3-epoxy-4-octene (11b).** *t*-BuOK (425 mg, 3.8 mmol) was dissolved in 30 mL of THF and cooled to −78 °C. $C_4H_9(PPh_3)Br$ (1.4 g, 3.5 mmol) was added, and the yellow mixture was stirred for 20 min. Epoxy aldehyde **10** (652 mg, 3.4 mmol), in THF (8 mL), was added slowly, and the mixture was stirred at −78 °C for 2 h. After an additional 0.5 h at rt the reaction was quenched by addition of H_2O and the slurry extracted with Et_2O (3 × 20 mL). The organic layer was washed with brine, dried, and concentrated. After purification of the concentrate by flash chromatography (90/10 pentane/ether), 422 mg (54%) of colorless oil was obtained: ^{1}H NMR δ 7.75 (m, 5 H), 5.76 (dd, J = 7.5, 4.0, 1 H), 5.17 (dd, J = 7.5, 3.0, 1 H), 4.61 (d, J = 12, 1 H), 4.59 (d, J = 12, 1 H), 3.72 (dd, J = 4.2, 3.0, 1 H), 3.69 (dd, J = 11.2, 4.0, 1 H), 3.54 (dd, J = 11.2, 6.3, 1 H), 3.36 (ddd, J = 6.3, 4.0, 4.2, 1 H), 2.18 (m, 2 H), 1.42 (m, 2 H), 0.93 (t, J = 7.0, 3 H); ^{13}C NMR δ 137.9, 133.7, 128.4, 127.8, 127.7, 123.2, 73.2, 68.5, 56.8, 51.9, 29.8, 22.6, 13.7; IR 3030, 2959, 2929, 2870, 1454, 1200, 1096, 1028, 913, 839 cm^{-1}.

(4*E*)-(2*S*,3*R*)-1-(Benzyloxy)-2,3-epoxy-4-nonene (11c). *t*-BuOK (0.85 mg, 0.75 mmol) was dissolved in 8 mL of THF, and the solution was cooled to −78 °C. Pentyltriphenylphosphonium bromide (425 mg, 0.67 mmol) was added, and the resulting orange solution was stirred for 10 min. Aldehyde **10** (120 mg, 0.63 mmol) in THF (1 mL) was added dropwise. The reaction was allowed to reach rt and then continued for a further 2.5 h. The mixture was partitioned between ether and brine. Drying and concentration afforded a yellow oil. Flash chromatography (SiO_2, pentane/ether 80/20) gave 124 mg (80%) of the pure product: ^{1}H NMR δ 7.37 (m, 5 H), 5.77 (dt, J = 11.0, 6.9, 1 H), 5.16 (dd, J = 11.0, 8.4, 1 H), 4.61 (dd, J = 11.5, 4.2, 1 H), 4.54 (dd, J = 11.5, 4.2, 1 H) 3.70 (m, 2 H), 3.56 (dd, J = 8.4, 6.3, 1 H), 3.38 (dt, J = 6.3, 4.2, 1 H), 2.2 (m, 2 H), 1.38 (m, 4 H), 0.92 (t, J = 6.5, 3 H); ^{13}C NMR δ 138.1, 137.9, 128.5, 128.4, 127.8, 122.9, 73.2, 68.5, 56.8, 51.9, 31.6, 27.5, 22.2, 13.9; IR 3069, 3030, 2950, 2930, 2860, 1598, 1454, 1345, 1160, 1093 cm^{-1}; $[\alpha]^{25}_D$ −62.9° (c 1.1, $CHCl_3$).

(3*E*)-(2*R*,5*S*)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)-3-hexen-2-ol (12a). $Pd(PPh_3)_4$ (85 mg, 0.07 mmol), NaNHTs (340 mg, 1.76 mmol), and NH_2Ts (302 mg, 1.77 mmol) were dissolved in 12 mL of CH_3CN under an argon atmosphere. Vinyl epoxide **11a** (300 mg, 1.46 mmol) in 3 mL of CH_3CN was added, and the mixture was heated at 40 °C for 3 h. The reaction mixture was cooled to rt, filtered, and diluted with Et_2O. The resulting solution was washed with brine containing 2% NaOH, NH_4Cl, and again with brine. After drying and concentration the yellow oily residue was purified by flash chromatography (SiO_2, pentane/ether, 70/30). Product **12a** was isolated in 86% yield (747 mg): ^{1}H NMR δ 7.78 (2 H, Ts), 7.35 (2 H, Ts), 7.30 (m, 5 H), 5.60 (dd, J = 15.0, 5.5, 1 H), 5.47 (dd, J = 15.0, 6.0, 1 H), 4.75 (d, J = 9.0, 1 H), 4.60 (s, 2 H), 4.10 (m, 1 H), 3.91 (ddq, J = 6.0, 9.0, 7.2, 1 H), 3.38 (dd, J = 10.1, 3.1, 1 H), 3.22 (dd, J = 10.1, 6.0, 1 H), 2.42 (s, 3 H), 2.35 (s, 1 H), 1.15 (d, J = 7.2, 3 H); ^{13}C NMR δ 143.1, 138.2, 137.8, 129.5 (2 C), 128.6, 128.4, 127.8, 127.7, 127.1, 73.9, 73.3, 70.3, 50.7, 21.7, 21.4; IR 3470, 3272, 3090, 2867, 1735, 1598, 1437, 1327, 1158 cm^{-1}; $[\alpha]^{25}_D$ −25.2° (c 0.8, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}NSO_4$: C, 63.99; H, 6.71. Found: C, 63.57; H, 6.98.

(3*E*)-(2*R,5*S**)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)-3-octen-2-ol (12b).** $Pd(PPh_3)_4$ (80 mg, 0.07 mmol), NaNHTs (300 mg, 1.5 mmol), and NH_2Ts (220 mg, 1.3 mmol) were dissolved in CH_3CN (10 mL). Vinyl epoxide **11b** (300 mg, 1.3 mmol) in 2 mL of CH_3CN was added and the mixture heated to 40 °C for 6 h. After being cooled to rt, the mixture was filtered and diluted with hexane/EtOAc (70/30). The yellow solution was washed with brine containing 2% NaOH, NH_4Cl, and again with brine. Back-extraction of the combined aqueous phases with ether, drying, and concentration of the combined organic layers afforded a thick yellow oil. Flash chromatography (SiO_2, hexane/EtOAc 70/30) gave **12b** in 67% yield (375 mg). ^{1}H NMR δ 7.72 (2 H, Ts), 7.31 (m, 5 H), 7.29 (2 H, Ts), 5.47 (dd, J = 15.0, 7.0, 1 H), 5.35 (dd, J = 15.0, 5.5, 1 H), 4.82 (d, J = 8.0, 1 H), 4.52 (s, 2 H), 4.15 (m, 1 H), 3.74 (m, 1 H), 3.32 (dd, J = 9.5, 3.5, 1 H), 3.14 (dd, J = 9.5, 8.0, 1 H), 2.42 (s, 3 H), 1.42 (m, 2 H), 1.26 (m, 2 H), 0.81 (t, J = 7.0, 3 H); ^{13}C NMR δ 143.2, 137.8, 130.1, 129.5, 128.5, 128.4, 127.9, 127.7, 127.3, 126.5, 74.0, 73.4, 70.4, 55.2, 38.0, 21.4, 18.6, 13.6; IR 3470, 3271, 3062, 2957, 2926, 2870, 2359, 1598, 1496, 1453, 1437, 1329, 1160, 1119, 1094, 1028 cm^{-1}.

(3*E*)-(2*R*,5*S*)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)-3-nonen-2-ol (12c). $Pd(PPh_3)_4$ (666 mg, 0.58 mmol) and 50 mL of CH_3CN were combined in a flask under an argon atmosphere. NaNHTs (155 mg, 8.0 mmol) and NH_2Ts (626 mg, 3.66 mmol) were added, and after 5 min **11c** (1.8 g, 7.3 mmol) in 5 mL of CH_3CN was added. The mixture was stirred at 40 °C for 14 h. After being cooled to rt, the mixture was filtered and washed with two portions of brine containing 2% NaOH and one portion of NH_4Cl. Back-extraction, washing of the combined organic phases with brine, drying, and concentration afforded crude product as a thick brown oil. Flash chromatography (SiO_2, pentane/ether 70/30 followed by EtOAc) afforded 2.12 g (68%) of pure product: ^{1}H NMR δ 7.71 (2 H, Ts), 7.35 (2 H, Ts), 7.25 (m, 5 H), 5.50 (dd, J = 15.0, 7.0, 1 H), 5.37 (dd, J = 15.0, 5.5, 1 H), 4.52 (s, 2 H), 4.46 (d, J = 7.7, 1 H) 4.17 (m, 1 H), 3.76 (ddt, J = 5.3, 7.7, 7.0, 1 H), 3.34 (dd, J = 9.5, 8.0, 1 H), 3.14 (dd, J = 9.5, 8.0, 1 H), 2.35 (s, 3 H), 2.28 (s, 1 H), 1.43 (m, 2 H), 1.21 (m, 4 H), 0.81 (t, J = 7, 3 H); ^{13}C δ 143.0, 138.2, 137.6, 131.9, 129.7, 129.3, 128.4, 127.7, 127.6, 127.1, 73.8, 73.2, 70.3, 55.2, 35.4, 23.3, 22.1, 21.4, 13.7; IR 3772, 3376, 3101, 3079, 2944, 2886, 1485, 1388, 1377, 1137, 1034, 995, 485 cm^{-1}; $[\alpha]^{25}_D$ −13.3° (c 0.3, $CHCl_3$).

(2*R*,3*S*)-4-(Benzyloxy)-2,3-epoxybutanal (14). Using the procedure outlined for **10b**, 2.1 g (0.011 mol) of **13** was oxidized with 1.9 g (0.016 mol) of NMO and 190 mg (0.054 mmol, 5 mol %) of TPAP in the presence of 0.63 g of crushed 4 Å molecular sieves. The yield of pure **14** was 1.37 g (65%): ^{1}H NMR δ 9.05 (d, J = 6.4, 1 H), 7.32 (m, 5 H), 4.61 (d, J = 12, 1 H), 4.59 (d, J = 12, 1 H), 3.85 (dd, J = 11.5, 2.7, 1 H), 3.59 (dd, J = 11.5, 5.0, 1 H), 3.48 (dt, J = 5.0, 2.0, 1 H), 3.34 (dd, J = 7.3, 2.0, 1 H); ^{13}C NMR δ 197.5, 137.3, 128.5, 128.0, 127.7, 73.5, 68.3, 56.2, 55.1; IR 3366, 3030, 2928, 2865, 1746, 1364, 1164, 1120, 909, 696 cm^{-1}; $[\alpha]^{25}_D$ +56.5° (c 1.16, $CHCl_3$).

(4*Z*)-(2*S,3*S**)-1-(Benzyloxy)-2,3-epoxy-4-hexene (15a).** Compound **15a** was synthesized by the same procedure as used for **11a** using 100 mg (0.52 mmol) of **14**, 70 mg (0.062 mmol) of *t*-BuOK, and 230 mg (0.062 mmol) of $C_2H_5(PPh_3)Br$. The yield was 63.6 mg (60%) and the *Z*:*E* ratio 89:11: ^{1}H NMR δ 7.30 (m, 5 H), 5.81 (ddd, J = 11.0, 7.0, 4.5, 1 H), 5.01 (ddq, J = 11.0, 1.5, 7.0, 1 H), 4.53 (d, J = 12, 1 H), 4.48 (d, J = 12, 1 H), 3.70 (dd, J = 11.0, 2.5, 1 H), 3.68 (dd, J = 11.0, 3.5, 1 H), 3.47 (m, 1 H), 3.04 (m, 1 H), 1.72 (dd, J = 8.0, 1.8, 3 H); ^{13}C NMR δ 138.5, 132.2, 129.1, 128.4 (2C), 127.6, 74.0, 70.6, 59.1, 52.1, 14.1; IR 3026, 2921, 2856, 1724, 1496, 1360, 1102, 815, 735, 698 cm^{-1}.

(4*Z*)-(2*S,3*S**)-1-(Benzyloxy)-2,3-epoxy-4-octene (15b).**

Using the same procedure described for compound **11a**, 192 mg (1.17 mmol) of **14**, 134 mg (0.034 mmol) of *t*-BuOK, and 720 mg of (1.80 mmol) $C_4H_9(PPh_3)Br$ were reacted in 13 mL of THF. The olefin **15b** was obtained in 70% yield (190 mg) and an *Z*:*E* ratio of 92:8: ^1H NMR δ 7.37 (m, 5 H), 5.74 (dt, J = 11.0, 7.2, 1 H), 5.08 (dd, J = 11.0, 8.8, 1 H), 4.62 (d, J = 12, 1 H), 4.57 (d, J = 12, 1 H) 3.78 (dd, J = 3.1, 11.5, 1 H), 3.52 (m, 1 H), 3.09 (ddd, J = 5.5, 3.1, 2.2, 1 H), 2.18 (m, 2 H), 1.42 (m, 2 H), 0.91 (t, J = 7.0, 3 H); ^{13}C NMR δ 137.9, 137.1, 128.4, 127.7, 127.6, 126.3, 73.3, 70.0, 58.5, 51.7, 29.7, 22.7, 13.6; IR 3015, 2928, 2864, 1746, 1494, 1364, 1102, 697 cm^{-1}.

(4*Z*)-(2*S*,3*S*)-1-(Benzyloxy)-2,3-epoxy-4-nonene (15c). Compound **15c** was synthesized by the procedure outlined for compound **11a** using 192 mg (1.17 mmol) of **14** and 134 mg (0.034 mmol) of *t*-BuOK 500 mg (1.21 mmol) of $C_5H_{11}(PPh_3)$-Br. **15c** was isolated in 78% yield (190 mg) and with a *Z*:*E* ratio of 92:8: ^1H NMR δ 7.37 (m, 5 H,), 5.74 (dt, J = 11.0, 7.5, 1 H), 5.06 (ddt, J = 10.5, 9.0, 1.5, 1 H), 4.61 (d, J = 12, 1 H), 4.57 (d, J = 12, 1 H) 3.77 (dd, J = 3.0, 11.5, 1 H), 3.54 (m, 2 H), 3.10 (ddd, J = 5.5, 3.0, 2.2, 1 H), 2.21 (m, 2 H), 1.38 (m, 4 H), 0.91 (t, J = 7.3, 3 H); ^{13}C NMR δ 137.9, 137.3, 128.5(2 C), 127.7, 126.1, 73.3, 70.0, 58.5, 51.7, 31.7, 27.4, 22.2, 13.9; IR 3016, 2945, 2818, 1693, 1453, 1364, 1102, 1028 cm^{-1}; $[\alpha]^{25}_D$ −28.8° (*c* 1.08, $CHCl_3$)

(3*E*)-(2*R,5*R**)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)-3-hexen-2-ol (16a).** Amido alcohol **16a** was synthesized from **15a** via the palladium-catalyzed reaction described for compound **12**. Thus, 140 mg (0.69 mmol) of **15a** was reacted with 140 mg (0.82 mmol) of H_2NTs, 160 mg (0.83 mmol) of NaHNTs, and 40 mg (0.035 mmol, 5 mol %) of $Pd(PPh_3)_4$. A total of 230 mg (89%) of **16a** was isolated: ^1H NMR δ 7.78 (2 H, Ts), 7.35 (2 H, Ts), 7.30 (m, 5 H), 5.68 (dd, J = 15.0, 6.2, 1 H), 5.44 (dd, J = 15.0, 5.3, 1 H), 5.01 (s, 1 H), 4.52 (s, 2 H), 4.19 (m, 1 H), 3.91 (ddq, J = 5.3, 8.0, 6.7, 1 H), 3.38 (dd, J = 9.5, 3.2, 1 H), 3.21 (dd, J = 9.5, 8.0, 1 H), 2.42 (s, 3 H), 2.57 (m, 1 H), 1.16 (d, J = 6.7, 3 H); ^{13}C NMR δ 143.3, 133.0, 129.6, 129.2, 128.5, 128.4, 127.9, 127.7, 127.1, 127.0, 73.8, 73.3, 70.3, 50.8, 21.7, 21.5; IR 3502, 3282, 3015, 2975, 2863, 1598, 971, 697 cm^{-1}.

(3*E*)-(2*R,5*R**)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)-3-octen-2-ol (16b).** Using the procedure outlined for compound **12**, 63 mg (0.27 mmol) of **15b**, 19 mg (0.016 mmol, 5 mol %) of $Pd(PPh_3)_4$, 56 mg (0.33 mmol) of H_2NTs, and 63 mg (0.33 mmol) of NaHNTs were combined in 3 mL of CH_3CN. A total of 88 mg (81%) of **16b** was obtained: ^1H NMR δ 7.71 (2 H, Ts), 7.35 (2 H, Ts), 7.25 (m, 5 H), 5.50 (dd, J = 15.0, 6.2, 1 H), 5.37 (dd, J = 15.0, 4.8, 1 H), 4.52 (s, 2 H), 4.62 (d, J = 8.0, 1 H) 4.17 (m, 1 H), 3.76 (ddt, J = 4.8, 8.0, 7.2, 1 H), 3.34 (dd, J = 9.5, 3.2, 1 H), 3.15 (dd, J = 9.5, 7.8, 1 H), 2.35 (s, 3 H), 2.28 (s, 1 H), 1.43 (m, 2 H), 1.21 (m, 2 H), 0.81 (t, J = 7.2, 3 H); ^{13}C NMR δ 145.1, 140.2, 139.7, 133.8, 131.9, 131.5, 130.5, 129.9, 129.7, 129.2, 75.8, 75.3, 72.4, 57.3, 39.8, 23.5, 20.6, 15.6; IR 3016.5, 2959, 2934, 2873, 1599, 1452, 1325, 1159, 1094, 1029, 668 cm^{-1}.

(3*E*)-(2*R*,5*R*)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)-3-nonen-2-ol (16c). Compound **16c** was synthesized by the procedure outlined for **12.** Thus, 190 mg (0.77 mmol) of **15c**, 44 mg (0.038 mmol, 5 mol %) of $Pd(PPh_3)_4$, 160 mg (0.94 mmol) of H_2NTs, and 180 mg (0.93 mmol) of NaHNTs were combined in 8 mL of CH_3CN giving 290 mg (91%) of **16c**: ^1H NMR δ 7.71 (2 H, Ts), 7.35 (2 H, Ts), 7.32 (m, 5 H), 5.48 (dd, J = 15.5, 6.5, 1 H), 5.35 (dd, J = 15.5, 5.5, 1 H), 4.90 (d, J = 7.7, 1 H), 4.50 (s, 2 H), 4.14 (m, 1 H), 3.72 (app quint, J = 7.0, 1 H), 3.31 (dd, J = 3.5, 9.5, 1 H), 3.14 (dd, J = 9.5, 8.0, 1 H), 2.43 (d, J = 3.5, 1 H), 2.37 (s, 3 H), 1.43 (m, 2 H), 1.18 (m, 4 H), 0.80 (t, J = 7.0, 3 H); ^{13}C NMR δ 143.0, 138.2, 137.7, 131.8, 129.9, 129.5, 128.5, 127.9, 127.7, 127.2, 73.8, 73.4, 70.3, 55.4, 35.4, 27.4, 22.2, 21.5, 13.8. IR 3489, 3274, 3028, 2930, 2861, 1654, 1496, 1324, 1160, 1094, 754, 666 cm^{-1}; $[\alpha]^{25}_D$ +9.9° (*c* 1.55, $CHCl_3$).

(2*R*,5*S*)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)hexan-2-ol (17a). The amidoalkenol **12a** (100 mg, 0.27 mmol) was dissolved in 5 mL of EtOH, and PtO_2 (4 mg, 0.02 mmol) was added. Hydrogen (1 atm) was applied, and the reaction was stirred at rt for 20 min. The catalyst was removed by filtration through Celite, and the solvent was evaporated. The colorless alkanol was obtained in 95% yield (95 mg): ^1H NMR δ 7.78 (2 H, Ts), 7.4−7.32 (m, 7 H), 4.88 (d, J = 8.0, 1 H), 4.55 (s, 2 H), 3.72 (m, 1 H), 3.40 (dd, J = 10.1, 3.0, 1 H), 3.31 (m, 1 H), 3.25 (dd, J = 10.1, 8.0, 1 H), 2.42 (s, 3 H), 1.8−1.2 (several multiplets, 4 H), 1.07 (d, J = 7.0, 3 H); ^{13}C NMR δ 143.0, 138.3, 137.9, 129,5, 128.4, 127.9, 127.7, 127.0, 74.4, 73.4, 69.9, 49.9, 33.1, 28.7, 21.9, 21.4; IR 3489, 3276, 3063, 3030, 2926, 2860, 1722, 1598, 1495, 1453, 1184 cm^{-1}; $[\alpha]^{25}_D$ −15.5° (c 0.8, $CHCl_3$). Anal. Calcd for $C_{20}H_{27}NSO_5$: C, 63.64; H, 7.2. Found: C, 63.50; H, 7.13.

(2*R,5*S**)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)-nonan-2-ol (17c).** Amido alcohol **12c** (2.3 g, 5.5 mmol) was dissolved in 50 mL of 99.5% EtOH. PtO_2 (172 mg, 0.75 mmol) was added, and a hydrogen pressure of 1 atm was applied. The heterogeneous system was stirred at rt for 7 h. The catalyst was removed by filtration through Celite, and the organic layer was concentrated. ^1H NMR of the crude product showed no starting material, and the product was isolated in 96% (2.22 g) yield: ^1H NMR δ 7.71 (2 H, Ts), 7.35 (2 H, Ts), 7.25 (m, 5 H), 4.79 (d, J = 7.5, 1 H), 4.56 (s, 2 H), 3.68 (dtt, J = 8.0, 3.0, 3.3, 1 H), 3.35 (dd, J = 3.0, 8.0, 1 H), 3.19 (dd, J = 3.0, 8.0, 1 H), 3.18 (m, 1 H), 2.49 (d, J = 3.3, 1 H), 2.35 (s, 3 H), 1.5−1.05 (several multiplets, 10 H), 0.89 (t, J = 6.1, 3 H); ^{13}C NMR δ 142.9, 138.3, 137.8, 129.4, 128.4, 127.8, 127.7, 127.0, 74.4, 73.3, 73.2, 69.9, 53.8, 58.3, 35.0, 30.5, 28.3, 27.3, 13.8; IR 3470, 3280, 3030, 2980, 2880, 1460, 1325, 1162, 1088, 812, 663 cm^{-1}.

(2*S*,5*S*)-2-[(Benzyloxy)methyl]-5-methyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (19a). Alcohol **17a** (410 mg, 1.1 mmol) was dissolved in 11 mL of THF, and Et_3N (300 μL, 2.2 mmol) was added. The mixture was cooled to 0 °C, and MsCl (120 μL, 1.6 mmol) was added dropwise. The reaction was allowed to reach rt and was then stirred for 2 h. The mixture was partitioned between ether and brine, dried, and concentrated. No further purification was performed, and the crude product was used directly in the cyclization reaction. The crude mesylate was dissolved in 20 mL of MeOH, and K_2CO_3 (800 mg, 5.8 mmol) was added. The reaction was stirred at rt overnight. The mixture was concentrated, diluted with water, and extracted three times with EtOAc. After drying and concentration the product was purified by flash chromatography (SiO_2, pentane/ether 80/20). The pure tosylpyrrolidine **19a** was isolated (312 mg, 80% overall yield from **17a**): ^1H NMR δ 7.75 (2 H, Ts), 7.38−7.20 (m, 7 H), 4.57 (s, 2 H), 3.79 (m, 2 H), 3.65 (m, 1 H), 3.47 (m, 1 H), 2.42 (s, 3 H), 1.87 (m, 1 H), 1.64 (m, 1 H), 1.55 (m, 2 H), 1.32 (d, J = 6.5, 3 H); ^{13}C NMR δ 143.2, 138.4, 137.9, 120.6, 128.4, 127.7, 127.6, 127.0, 73.5, 60.7, 57.8, 57.7, 32.3, 27.5, 22.9, 21.4; IR 3080, 3040, 2967, 2868, 1598, 1494, 1453, 1343, 1208, 1161, 1092, 1044 cm^{-1}; $[\alpha]^{25}_D$ −84.9° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{25}NSO_3$: C, 66.82; H, 7.01. Found: C, 66.93, H, 7.04.

(2*S,5*S**)-2-[(Benzyloxy)methyl]-5-butyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (19c).** Amido alcohol **17c** (800 mg, 1.92 mmol) and Et_3N (520 μL, 3.7 mmol) were dissolved in THF (15 mL) and cooled to 0 °C. Mesyl chloride (260 μL, 3.4 mmol) was added dropwise, and the reaction was stirred at 0 °C for 1 h and then at rt for a further 3.5 h. The reaction was quenched by pouring the mixture into 50 mL of H_2O. The aqueous phase was extracted with three 50 mL portions of ether. The combined organic layers were washed with brine, dried, and concentrated to give 914 mg of product which was used directly for cyclization. Mesylate **17c** from above was dissolved in MeOH (40 mL), and K_2CO_3 (1.7 g, 12.3 mmol) was added. The reaction was stirred at rt for 12.5 h. The solvent was removed in vacuo and the solid residue dissolved in brine. The water phase was extracted three times with 30 mL of ether. After combination the organic layers were washed with brine, dried, and concentrated. An 806 mg portion of **19c** was isolated as a pale yellow oil. The overall yield from **17c** was 91%: ^1H NMR δ 7.71 (2 H, Ts), 7.35 (2 H, Ts), 7.3 (m, 5 H), 4.56 (s, 2 H), 3.78 (m, 2 H), 3.54 (m, 1 H), 3.45 (m, 1 H), 2.41 (s, 3 H), 2.00−0.80 (several multiplets, 13 H); ^{13}C NMR δ 143.3, 138.3, 134.7, 129.6, 128.4, 128.0, 127.7, 127.6, 77.2, 73.4, 62.0, 60.3, 36.4, 29.6, 28.4, 27.6, 22.6, 21.5, 14.1; IR 3070, 3030, 2955, 2930, 2860, 1495, 1453, 1344, 1207, 1160, 1093, 1034, 665 cm^{-1}.

(2S,5S)-2-[(Benzyloxy)methyl]-5-methylpyrrolidine (20). Na(Hg) 6% (480 mg) was added to a solution of tosylpyrrolidine **18a** (50 mg, 0.14 mmol) and Na_2HPO_4 (180 mg, 1.3 mmol) in 1.5 mL of MeOH. The mixture was heated to 50 °C for 18 h. After being cooled to rt the mixture was filtered through Celite, and the Celite was washed with EtOAc. Brine was added to the mixture, and the layers were separated. Extraction with EtOAc, drying, and concentration of the combined organic layers afforded 24 mg (89% yield) of pure pyrrolidine **20**: ^{1}H NMR δ 7.33 (m, 5 H), 4.53 (s, 2 H), 3.52 (dd, J = 9.0, 4.5, 1 H), 3.41 (dd, J = 9.0, 6.5, 1 H), 3.30 (m, 1 H), 3.13 (m, 1 H), 1.94 (m, 1 H), 1.82 (m, 2 H), 1.50 (m, 2 H), 1.16 (d, J = 6.0, 3 H); ^{13}C NMR δ 138.6, 128.3, 127.7, 127.5, 74.4, 73.3, 58.6, 54.6, 33.1, 28.2, 21.4; IR 3350, 3029, 2958, 2866, 1496, 1454, 1366, 1206, 1100, 1028 cm^{-1}; $[\alpha]^{25}_D$ +2.5° (*c* 1.1, $CHCl_3$).

(2S,5S)-2-(Hydroxymethyl)-5-methylpyrrolidine (7). Pyrrolidine **20** (60 mg, 0.32 mmol) was dissolved in MeOH (1 mL) to which was added 5% palladium on carbon (16 mg) and $MeSO_3H$ (10 μL). A hydrogen pressure of 1 atm was applied, and the reaction was stirred for 3 h at rt. The reaction mixture was filtered through Celite, and the MeOH was removed in vacuo. The resulting oil was dissolved in CH_2Cl_2 and filtered through a plug of Na_2CO_3. Concentration of the CH_2Cl_2 filtrate afforded 34 mg (92%) of product **7** as a pure colorless thick oil: ^{1}H NMR δ 3.59 (m, 1 H), 3.38 (m, 2 H), 3.36 (m, 1 H), 3.24 (m, 1 H), 2.20–2.00 (m, 2 H), 1.82 (m, 2 H), 1.58 (m, 1 H), 1.24 (m, 1 H), 1.09 (d, J = 6.6, 3 H); ^{13}C NMR δ 62.0, 57.5, 50.8, 39.3, 31.3, 17.3; $[\alpha]^{25}_D$ +8.8° (*c* 0.4, EtOH).

(2R*,5R*)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)hexan-2-ol (21a). Using the same procedure as outlined for **17**, hydrogenation of 200 mg (0.61 mmol) of **16a** in the presence of 80 mg (0.035 mmol) of PtO_2 gave 175 mg (76%) of **21a**: ^{1}H NMR δ 7.71 (2 H, Ts), 7.35 (2 H, Ts), 7.25 (m, 5 H), 4.65 (d, J = 8.0, 1 H), 4.52 (s, 2 H), 3.70 (m, 1 H), 3.42 (dd, J = 3.2, 9.2, 1 H), 3.33 (m, 1 H), 3.27 (dd, J = 9.2, 8.0, 1 H), 2.40 (s, 1 H), 2.35 (s, 3 H), 1.5–1.05 (several multiplets, 10 H), 0.89 (t, J = 6.5, 3 H); ^{13}C NMR δ 143.1, 137.8, 138.1, 129.6, 128.5, 127.9, 127.7, 127.1, 74.3, 73.4, 70.2, 50.0, 33.5, 28.8, 21.7, 21.5; IR 3504, 3286, 3017, 2928, 1159, 1094, 697 cm^{-1}.

(2R,5R)-1-(Benzyloxy)-5-(*p*-toluenesulfonamido)nonan-2-ol (21c). Compound **21c** was prepared from **16c** by the same procedure as described for **17a**. Thus, 190 mg (0.45 mmol) of **16c** and 50 mg (0.022 mmol) of PtO_2 were combined in MeOH under hydrogen to give 179 mg (95%) of **21c**: ^{1}H NMR δ 7.71 (2 H, Ts), 7.35–7.20 (m, 5 H), 4.90 (d, J = 8.5, 1 H), 3.63 (m, 1 H), 3.35 (dd, J = 9.5, 3.0, 1 H), 3.20 (dd, J = 9.3, 8.1, 1 H), 3.16 (m, 1 H), 2.38 (s, 3 H), 1.38–1.21 (m, 5 H), 1.08 (m, 5 H), 0.72 (t, J = 7.0, 3 H); ^{13}C NMR δ 142.9, 138.4, 137.8, 129.5, 128.5, 127.8, 127.7, 127.0, 74.3, 73.3, 70.4, 54.0, 34.7, 31.2, 28.6, 27.4, 22.4, 21.5, 13.8; IR 3482, 3281, 2930, 2860, 1452, 1323, 1159, 1094, 754, 666 cm^{-1}; $[\alpha]^{25}_D$ +9.3 (*c* 1.66, $CHCl_3$).

(2S*,5R*)-2-[(Benzyloxy)methyl]-5-methyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (23a). Using the same procedure as described for **19a**, 100 mg (0.27 mmol) of **21a** was reacted with 41 μL (0.053 mmol) of MsCl and 70 μL (0.050 mmol) of Et_3N in 5 mL of THF, followed by 200 mg (1.45 mmol) of K_2CO_3 in 5 mL of MeOH. The yield of **23a** was 88 mg (89%): ^{1}H NMR δ 7.71 (2 H, Ts), 7.35 (2 H, Ts), 7.25 (m, 5 H), 4.43 (d, J = 12, 1 H), 3.37 (d, J = 12, 1 H), 4.06 (m, 1 H), 3.99 (m, 1 H), 3.70 (dd, J = 3.3, 9.5, 1 H), 3.47 (m, 1 H), 2.40 (s, 3 H), 1.64 (m, 1 H), 1.47 (m, 2 H), 1.17 (m, 2 H), 1.22 (m, 3 H); ^{13}C NMR δ 142.6, 139.3, 129.5, 129.3, 128.3, 127.5, 127.4, 126.9, 73.1, 71.2, 59.2, 56.9, 31.5, 28.9, 21.4, 21.0; IR 3028, 2966, 2864, 1598, 1453, 1341, 1157, 1100, 733, 666 cm^{-1}.

(2S,5R)-2-[(Benzyloxy)methyl]-5-butyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (23c). Pyrrolidine **23c** was synthesized in accordance with the procedure described for **19a**. Thus, 150 mg (0.36 mmol) of **21c** was reacted with 60 μL (0.077 mmol) of MsCl and 200 μL (1.42 mmol) of Et_3N in 8 mL of THF, followed by 250 mg (1.8 mmol) of K_2CO_3 in 8 mL of MeOH. The yield of **23c** was 124 mg (86%): ^{1}H NMR δ 7.72 (2 H, Ts), 7.38–7.21 (m, 7 H), 4.42 (d, J = 12, 1 H), 4.36 (d, J = 12, 1 H), 4.00 (m, 1 H), 3.87 (m, 1 H), 3.73 (dd, J = 3.2, 9.5, 1 H), 3.47 (dd, J = 9.5, 7.5, 1 H), 2.38 (s, 3 H), 2.01 (m, 2 H), 1.35–1.05 (m, 6 H), 0.86 (t, J = 7.5, 3 H); ^{13}C NMR δ 142.6, 139.4, 138.2, 129.3, 128.2, 127.4, 127.3, 126.7, 72.9, 71.0, 61.4, 59.2, 33.4, 28.4, 27.9, 27.1, 22.5, 21.3, 13.9; IR 3029, 2956, 2927, 2860, 1341, 1157, 1098, 666 cm^{-1}; $[\alpha]^{25}_D$ −67.2° (*c* 1.10, $CHCl_3$)

(2S,5R)-2-(Hydroxymethyl)-5-butyl-*N*-(*p*-tolylsulfonyl)-pyrrolidine (8). In a 25 mL round bottom flask was dissolved 70 mg (0.20 mmol) of **23c** in 20 mL of MeOH. Pd/C (5%) (37 mg, mmol, 10 mol%) was added, and the flask was placed under 1 atm of H_2. After 3 h the catalyst was removed by filtration through Celite, and the reaction mixture was concentrated. The crude mixture was dissolved in 50 mL of EtOAc and washed with 20 mL of brine. The brine was back-extracted with 20 mL of EtOAc and dried over Na_2SO_4. Concentration of the organic layer afforded 51 mg (95%) of **8** as a clear thick oil. ^{1}H NMR δ 7.76 (2 H, Ts), 7.30 (2 H, Ts), 4.02 (m, br, 1 H), 3.75 (s, br, 3 H, 2 overlapping peaks), 2.61 (s, exch, 1 H), 2.44 (s, 3 H), 2.03 (m, 2 H), 1.87 (m, 2 H), 1.67 (m, 2 H) 1.35–1.04 (several m, 4 H), 0.85 (t, J = 7.1); ^{13}C NMR δ 143.0, 138.6, 129.5, 126.9, 65.2, 62.2, 61.5, 32.8, 28.4, 28.2, 28.1, 22.5, 21.4, 13.9; IR 3483, 2958, 2929, 1457, 1326, 1155, 1098, 1045, 756, 666 cm^{-1}; $[\alpha]^{25}_D$ −22.6° (*c* 1.09, $CHCl_3$).

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Supporting Information Available: NMR spectra of all compounds (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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