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Enantioselective Syntheses of *trans*-3,4-Difluoropyrrolidines and Investigation of Their Applications in Catalytic Asymmetric Synthesis†

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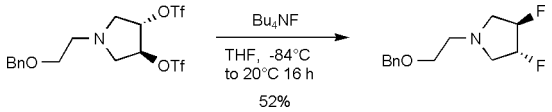

Asymmetric syntheses of enantiopure *trans*-3,4-difluoropyrrolidines have been prepared by the introduction of fluorine at both centers in a single operation; asymmetric epoxidations and additions to benzaldehyde were conducted using catalysts whose chirality depends on organofluorine asymmetry.

Introduction

Organofluorine compounds have achieved significance in many areas,[1] notably in the areas of materials[2] and bio-organic[3] chemistry and through their pharmaceutically desirable properties.[4−6] Many fluorinated α-amino acids are potent antitumor and antiviral agents,[1a,4a] and the incorporation of fluorinated amino acids into proteins is emerging as a valuable means of designing hyperstable protein folding, as well as inducing highly specific protein−protein interactions.[3] The significance of monofluoro analogues in biochemistry[1,7] is illustrated by the antimetabolite (2*R*,3*R*)-fluorocitric acid, an aconitase inhibitor that blocks the citric acid cycle.[5,7] Replacement of an sp^3 C−H bond by an sp^3 C−F bond often has little effect in terms of size but produces appreciably different electronic properties, leading to unusual conformational preferences such as the gauche effect,[8] observed in several types of fluorinated systems including 4-fluoro-L-proline.[9] Replacement of a C−H bond by a C−F bond can be a useful means of influencing conformation;[10] the spatial orientation of sp^3 C−F bonds in organofluorine compounds has also been identified as significant in many other fields, including nucleoside and carbohydrate chemistry, organic liquid crystals,[2c] and polymers.[11] Additionally, organofluorine ligands can be at least as powerful as oxygen ligands in coordinating metals.[12] In

† This contribution is dedicated to Professor Steven V. Ley on the occasion of his 60th birthday.

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many of the above areas, there is a need for defined stereochemistry at the carbon center(s) bearing fluorine; therefore, efficient means of controlling organofluorine stereochemistry are of considerable value.

Whereas enantiocontrolled syntheses of monofluoro-organic compounds are well established, syntheses of stereopure vicinal difluoro compounds are much scarcer,[13−15] especially those in enantiopure form.[16,17] The difficulty in forming C_2 symmetric difluorides is enhanced by the cis addition that is usually observed[18,19] when molecular fluorine adds to alkenes; where trans addition has been observed, yields are usually low.[19] Whereas nucleophilic displacement of single hydroxy groups is usually possible using fluoride sources such as diethylaminosulfur trifluoride (DAST),[20] few systems with additional proximate hydroxyl groups have been shown to undergo smooth fluorodehydroxylation. For example, DAST reacts with cyclohexane-1,2-diol to give only a trace of 1,2-difluorocyclohexanes, with loss of stereointegrity.[21] The reaction of SF_4 with enantiomerically pure tartaric acid leads to exchange of both hydroxy groups for fluorine, but with complete loss of optical activity, only the meso difluoro acid is formed.[22a] Similarly unsuccessful were attempts to react XeF_2 with tartrate esters.[14c] Notwithstanding such difficulties, we recently described[16a] the enantiocontrolled introduction of fluorine at two adjacent carbon stereocenters in a single operation, and here we describe the syntheses of enantiopure vicinal difluorides **5** and their participation as catalysts in two asymmetric processes.

Results and Discussion

Because attempted double vicinal displacements of tartaric acid derivatives by fluoride had not afforded the corresponding enantiopure vicinal difluorides,[22] displacements on cyclic systems derived from pyrrolidine-3,4-diols **3** were investigated in the present study. A typical route[23] to **3** involves the direct condensation of L-tartaric acid with an amine (RNH_2) to give the imide in modest yield followed by reduction with $LiAlH_4$. Improved protocols were sought because both steps have disadvantages, including difficulties in isolation or poor yields. In a representative procedure, (3*R*,4*R*)-diacetoxysuccinic anhydride (**1**)[24] was reacted with a primary amine (1 equiv) in THF at 0 °C, and the intermediate amido acid formed was treated directly with $SOCl_2$ (24 h, 20 °C) to give the diacetoxypyrrolidine-2,5-dione **2** in yields of 93% (**2a**), 71% (**2b**), and 93% (**2c**). Later work showed that the cyclization step could also be conducted using oxalyl chloride in DMF at −84 °C, by which method **2d** was prepared in 73% yield. The standard procedure of cyclodehydration using acetyl chloride requires long periods at reflux and in the examples studied here typically afforded poor yields of the imides **2**.

Efforts to reduce the imides **2** with a variety of reagents including lithium aluminum hydride, sodium borohydride−boron trifluoride−etherate,[25] and lithium triethylborohydride in the presence of boron trifluoride−etherate and triethylsilane[26] were unsuccessful. Modest success was achieved using THF·BH_3,[27] but removal of the residual boron adducts proved problematic. However, the pyrrolidine-2,5-diones **2** were successfully reduced with $NaBH_4$−I_2 in THF.[27] In a modification of the published procedure for the hydrolytic workup,[28] a two-stage workup involved stirring with 1:1 acetic acid−hydrochloric acid (10 M) for 10 h followed by washing with methanolic KOH (4 M).

With the diols **3** secured, it was envisaged that the corresponding 3,4-dimesylates might undergo 2-fold displacement because the mesylate of a 4-hydroxyproline derivative was displaced upon treatment with KF in hot DMF.[29] However, the dimesylate of diol **3a** gave no fluoro compound when treated with KF (5 equiv) in the presence of a catalytic amount of 18-crown-6 in DMF at 80 °C (14 days). Reaction of the same dimesylate with tetra-*n*-butylammonium fluoride (TBAF, 3 equiv) in THF at reflux gave only 1-cyclohexylpyrrole (84%), the product of two eliminations.

It was hoped that the ready eliminations during nucleophilic attack on the 3,4-disubstituted pyrrolidines could be suppressed by using the highly reactive bistrifluoromethanesulfonates (bistriflates). Indeed, reaction of the diols **3** with Tf_2O (2 equiv, 4 h, −85 °C) in the presence of pyridine (2 equiv) in dichloromethane afforded the bistrifluoromethanesulfonates **4**. These were

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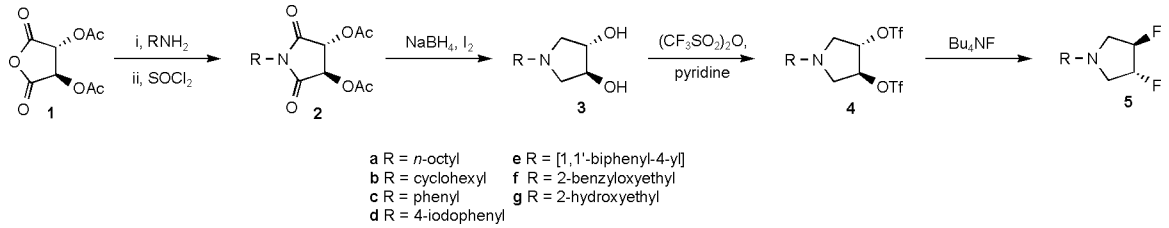
SCHEME 1



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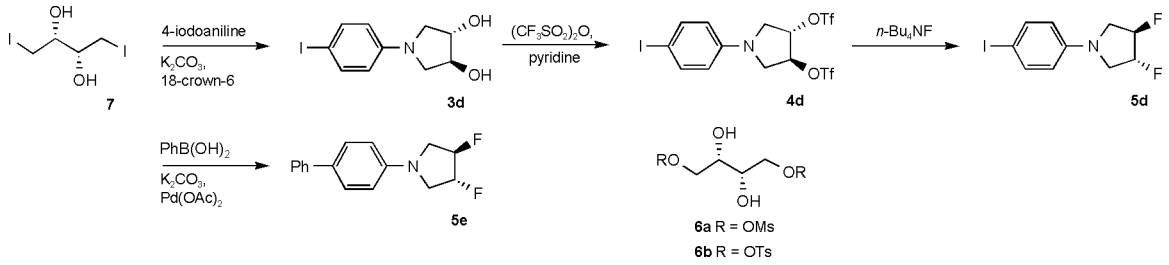
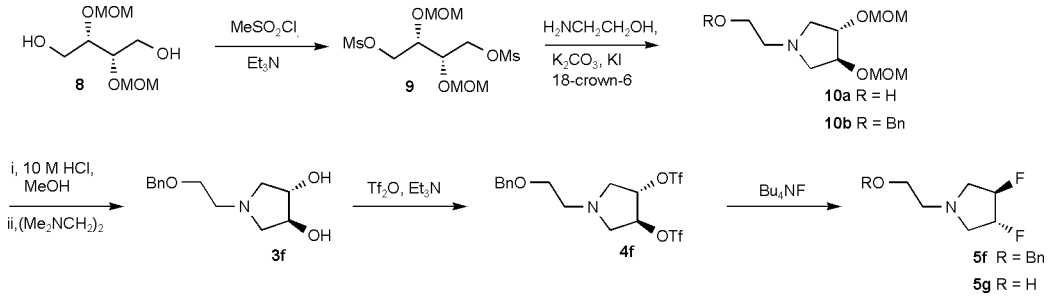


SCHEME 3



isolable in the cases of **4a** (R = *n*-octyl) and **4c** (R = Ph), but **4b** (R = cyclohexyl) decomposed rapidly during column chromatography. For the isolable cases, purification of the bistriflates by rapid flash column chromatography and eluting with solvents cooled to 5 °C was the preferred procedure and led to much purer difluorides **5**. The bistrifluoromethanesulfonates **4** were reacted with TBAF (3 equiv, 16 h, −85 °C to 20 °C) in THF, resulting in stereoselective introduction of fluorine with clean inversion at both centers to give the difluoropyrrolidines **5a**, **5b**, and **5c** in respective yields of 83, 42, and 76%.

Organofluorine compounds find extensive use in materials[11] and liquid crystal applications,[2] although to our knowledge a C_2 symmetric 1,2-difluorinated compound has not been prepared with such an application in mind. Consequently, it was of interest to prepare *N*-arylated derivatives of **5**. However, although the diol **3e** could be prepared in 18% from the corresponding imide **2e** (procedures as in Scheme 1), access to **5e** by this method was not possible because reaction of diol **3e** with Tf_2O did not afford the corresponding bistriflate **4e**. A modified approach was then examined, in which formation of **5d** would enable access to **5e** by a Suzuki coupling (Scheme 2). However, although the imide **2d** could be prepared from the anhydride **1** and 4-iodoaniline in 73% yield, reduction using $NaBH_4$−I_2 failed to provide any of the desired diol **3d**. Consequently, an alkylation approach was investigated in which 4-iodoaniline was reacted with the dimesylate **6a** in DMF at 100 °C and also with the ditosylate **6b** in DMF at 100 °C, but in neither case was the desired reaction achieved. In contrast, dialkylation using (2*R*,3*R*)-1,4-diiodobutane-2,3-diol (**7**) was successful by reaction with 4-iodoaniline in DMF at 90 °C giving **3d** in 34% yield. Using the procedures outlined in Scheme 1, we performed bistriflation of **3d** with Tf_2O in dichloromethane (1.05 equiv, 4 h, −85 °C) in the presence of pyridine (2.1 equiv) to afford **4d** (37%), which underwent the desired 2-fold displacement with TBAF (3 equiv, 16 h, −85 to 20 °C) in THF giving **5d** in 90% yield. A modified Suzuki coupling[30] of **5d** with phenylboronic acid in aqueous acetone in the presence of $Pd(OAc)_2$ and K_2CO_3 completed the synthesis of **5e**, albeit in only 24% yield.

An alkylation approach (Scheme 3) was also successful in affording the 2-oxyethyl derivatives **5f** and **5g**, the latter being tested in asymmetric alkylation of benzaldehyde (see below). The diol **8**, prepared by MOM protection of dimethyl L-tartrate and subsequent reduction with $LiAlH_4$,[31] was converted into the dimesylate **9** (49%) by reaction with mesyl chloride and Et_3N in dichloromethane at 0 °C. Dialkylation of ethanolamine was achieved with **9** by reaction with K_2CO_3 in the presence of a catalytic amount of 18-crown-6 in DMF at 100 °C (48 h), thus affording the hydroxyethylpyrrolidine **10a** (57%). Benzylation of **10a** using NaH followed by benzyl bromide in THF at reflux afforded the benzyl derivative **10b** (82%) which was deprotected with 10 M hydrochloric acid to give the diol **3f** (69%). Reaction of

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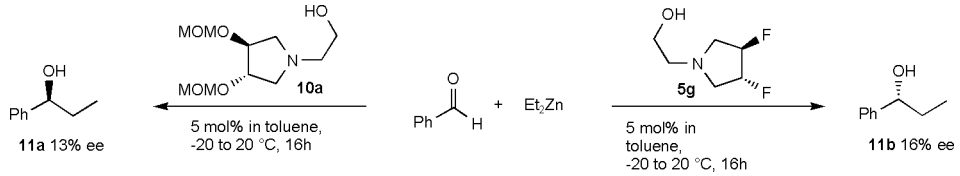
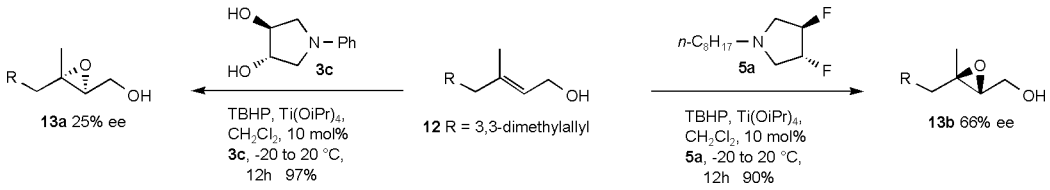
SCHEME 4



SCHEME 5



diol **3f** with Tf_2O in dichloromethane (2.1 equiv, 4 h, −85 °C) in the presence of Et_3N (2.1 equiv) afforded the bistriflate **4f** (42%) which underwent 2-fold displacement with TBAF (3 equiv, 16 h, −85 °C to 20 °C) in THF giving 1-(2-benzyloxyethyl)pyrrole (35%) and **5f** in 52% yield. The latter was debenzylated by treatment with $Me_2S{\cdot}BCl_3$ in dichloromethane at −85 °C and worked up with Me_2NEt to give (3*R*,4*R*)-1-(2-hydroxyethyl)-3,4-difluoropyrrolidine **5g** (66%).

The presence of fluorine ligands in catalytic organic reactions is an area of emerging importance.[32] In most cases, the asymmetry of an unrelated organic ligand (e.g., binol) has been the source of induction.[32] The enantioselective epoxidation of alkenes catalyzed by an α-fluorotropinone[33] and our previously disclosed asymmetric epoxidation[16a] are two of the few cases described in which induction depends on asymmetry derived from assembly around a C−F bond. Consequently, we wished to explore whether the present enantiopure and C_2 symmetric difluorides could be used in catalytic asymmetric synthesis. Addition of diethylzinc to benzaldehyde proceeds in high enantiomeric excess (ee) using various chiral ethanolamine catalysts, for which the reaction serves as a benchmark of the enantioselectivity of the catalyst; according to Soai's model,[34] coordination through both oxygen and nitrogen is necessary, and usually as part of a dimeric structure. This reaction (conditions in Scheme 4) was investigated using the fluoro alcohol **5g** as the catalyst, which in 2, 5, and 15 mol % afforded **13a** in 7, 16, and 16% ee, respectively. Although small, the asymmetric induction is opposite and similar in size to that afforded by 5 mol % of the nonfluorinated analogue **10a**, a process that almost certainly involves coordination of zinc to the pyrrolidine nitrogen atom. The effective size of the fluoro substituents is manifestly sufficient to afford appreciable asymmetric induction.

Catalysis of the epoxidation of geraniol by difluorides **5a** and **5b** has also been investigated (Scheme 5); reactions were conducted in dichloromethane using 15 mol % of $Ti(O^iPr)_4$ and 10 mol % of catalyst, the best result observed affording **13b** in 66% ee.[16a] These results show that for the catalytic asymmetric epoxidations in Scheme 5 fluoro substituents can provide enantioselection comparable with that of hydroxyl groups, although no mechanistic analogy is being proposed. Ligation via the nitrogen atom in **5g** is sufficient to induce ee in the case of ethylation of benzaldehyde and as such may also apply to **5** in the asymmetric epoxidations (Scheme 5). In Sharpless asymmetric epoxidations,[35] free hydroxyl groups on the catalyst (dialkyl tartrate) are a prerequisite for enantioselectivity, consistent with the dimeric catalyst model;[36] that requirement is in marked contrast to the difluorides **5**, whose lack of hydroxyl groups indicates a different mode of coordination to titanium(IV).

Although nucleophilic displacements of 3-chloropiperidines can proceed with retention of configuration by participation of the nitrogen atom in a bicycloazonium intermediate,[37] we are not aware of an analogy for the displacement of a 3-substituent on a pyrrolidine ring relevant to the present work. Although the absolute configuration of the 3,4-difluoropyrrolidines remains to be proved, the current evidence (optical rotations opposite and comparable with the diols and opposite asymmetric induction compared with diol derivatives; Scheme 4) is consistent and together with literature precedent for inversion in monofluoro systems[29] supports the configurations assigned on the basis of inversion at both stereogenic centers of the bistriflates.

Conclusions

3,4-Difluoropyrrolidines have been synthesized by a dependable 2-fold displacement of the corresponding bistriflates. The 2-fold displacement proceeds with excellent stereocontrol and consequently permits 3,4-difluoropyrrolidines to be obtained in either enantiomerically pure form. Several of the difluoropyrrolidines **5** displayed significant catalytic properties in asymmetric epoxidation and asymmetric alkylation of benzaldehyde, thus providing examples of asymmetric synthesis catalyzed by compounds whose chirality depends on organofluorine asymmetry. In addition, *N*-aryl-3,4-difluoropyrrolidines

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such as **5e** can be expected to exhibit interesting properties in connection with the liquid crystalline state.

Experimental Section

The following compounds were prepared according to literature procedures: (3*R*,4*R*)-3,4-diacetoxyfuran-2,5-dione (**1**),[24] (3*R*,4*R*)-3,4-diacetoxy-1-phenylpyrrolidine-2,5-dione (**2c**),[38] (3*S*,4*S*)-1-phenylpyrrolidine-3,4-diol (**3c**),[23b] (2*R*,3*R*)-1,4-bis-(methanesulfonyloxy)butane-2,3-diol (**6a**),[39] (2*S*,3*S*)-1,4-bis(4-methylphenylsulfonyloxy)butane-2,3-diol (**6b**),[40] (3*R*,4*R*)-1,4-diiodobutane-1,4-diol (**7**),[41] (2*S*,3*S*)-2,3-bis(methoxymethyloxy)-butane-1,4-diol (**8**),[42] and (4*S*,5*S*)-4,5-diiodomethyl-2,2-dimethyl-1,3-dioxolane.[43]

(3*R*,4*R*)-3,4-Diacetoxy-1-*n*-octylpyrrolidine-2,5-dione (2a). General Procedure A. To a stirred solution of (3*R*,4*R*)-3,4-diacetoxyfuran-2,5-dione (**1**) (20.0 g, 93 mmol) in 250 mL of anhydrous tetrahydrofuran at 0 °C under an atmosphere of dry nitrogen was added a solution of *n*-octylamine (12.0 g, 92.6 mmol) in 35 mL of dry tetrahydrofuran dropwise using a double-tipped needle of stainless steel. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for 16 h (consumption of **1** was confirmed by IR spectroscopy). To the stirred mixture cooled to −20 °C under an atmosphere of dry nitrogen was added dropwise a solution of thionyl chloride (44 g, 0.37 mol) in dry tetrahydrofuran (40 mL) using a double-tipped needle of stainless steel. The mixture was then allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for an additional 48 h. The mixture was quenched by the addition of saturated aqueous ammonium chloride (120 mL), and the aqueous layer was extracted with ethyl acetate (3 × 70 mL). The combined organic layers were washed with brine (2 × 70 mL) and dried over $MgSO_4$. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated under reduced pressure. The residue was dissolved in the minimum quantity of dichloromethane, applied to the top of a prepacked column of silica gel, and purified by flash chromatography (3:17 ethyl acetate/40−60 °C petroleum ether). The appropriate fractions were combined and filtered through a glass wool plug, and the eluent was evaporated under reduced pressure to give **2a** (28.2 g, 93%) as a pale yellow oil: $[\alpha]_D^{34}$ +71.8 (*c* 2.5, chloroform); IR ν_{max} (chloroform) 2990, 2905, 1760, 1740 cm^{-1}; ^1H NMR δ 5.51 (2H, s), 3.58 (2H, m), 2.21 (6H, s), 1.62 (2H, m), 1.28 (10H, m), 0.87 (3H, t, J = 7.0 Hz); ^{13}C NMR δ 169.9, 169.4, 72.8, 39.6, 31.8, 29.0, 29.0, 27.4, 26.7, 22.6, 20.4, 14.1; LRMS−FAB *m/e* (rel intensity %; positive *m*-$NO_2C_6H_5CO_2H$ MATRIX) 328 ($[M + H]^+$, 91), 286 (M^+, 100), 268 (59), 244 (83), 154 (13), 137 (41), 115 (21), 107 (24); HRMS−FAB calcd for $C_{16}H_{26}NO_6$ [M + H]$^+$ 328.1760, found 328.1751.

(3*R*,4*R*)-3,4-Diacetoxy-1-(4-iodophenyl)pyrrolidine-2,5-dione (2d). To a stirred solution of (3*R*,4*R*)-3,4-diacetoxyfuran-2,5-dione (**1**) (20.0 g, 93 mmol) in dry DMF (100 mL) at 0 °C under an atmosphere of dry nitrogen was added dropwise a solution of 4-iodoaniline (20.3 g, 92.6 mmol) in dry DMF (30 mL) using a double-tipped needle of stainless steel. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for 16 h (consumption of **1** was confirmed by IR spectroscopy). To the stirred mixture cooled to −85 °C under an atmosphere of dry nitrogen was added dropwise a solution of oxalyl chloride (23.5 g, 185 mmol) in dry dichloromethane (50 mL) using a double-tipped needle of stainless steel. The mixture was then allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for an additional 16 h. The mixture was quenched by the addition of aqueous lithium chloride (120 mL, 2.0 M), and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with brine (2 × 60 mL) and dried over $MgSO_4$. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated under reduced pressure. The residue was dissolved in the minimum quantity of dichloromethane, applied to the top of a prepacked column, and purified by flash chromatography over silica gel (3:7 ethyl acetate/40−60 °C petroleum ether). The appropriate fractions were combined and filtered through a glass wool plug, and the eluent was evaporated under reduced pressure to give **2d** (28.2 g, 73%) as a purple powder (mp 160−170 °C). A small sample was recrystallized from ethanol to give **2d** as pale blue prisms: mp 181−182 °C; $[\alpha]_D^{31}$ +59.4 (*c* 0.4, acetone); IR ν_{max} (KBr) 3050, 2950 (CH), 1725, 1735 (C=O), 1600, 1500 (Ph) cm^{-1}; ^1H NMR δ 7.81 (2H, J = 9.5 Hz), 7.11 (2H, J = 9.5 Hz), 5.61 (2H, s), 2.22 (6H, s); ^{13}C NMR δ 170.1, 168.2, 138.6, 130.6, 127.9, 94.9, 72.9, 20.4; LRMS−FAB *m/e* (rel intensity %; positive *m*-$NO_2C_6H_5CO_2H$ MATRIX) 418 ($[M + H]^+$, 100), 417 (M^+, 34), 376 (83), 358 (37), 334 (29), 307 (42), 289 (44). Anal. Calcd for $C_{14}H_{12}NO_6I$: C, 40.28; H, 2.87; N, 3.36; I, 30.46. Found: C, 40.36; H, 2.74; N, 3.06; I, 30.45.

(3*S*,4*S*)-1-*n*-Octylpyrrolidine-3,4-diol (3a). General Procedure B. To a rapidly stirred suspension of (3*R*,4*R*)-3,4-diacetoxy-1-octylpyrrolidine-2,5-dione (**2a**) (15.0 g, 45.9 mmol) and sodium borohydride (10.5 g, 275 mmol) in anhydrous tetrahydrofuran (500 mL) at 0 °C under an atmosphere of dry nitrogen was added dropwise a solution of iodine (35.0 g, 137 mmol) in dry tetrahydrofuran (100 mL) using a double-tipped needle of stainless steel. After addition, the mixture was heated slowly to reflux (consumption of **2a** was confirmed by IR spectroscopy). The mixture was then cooled to 0 °C and quenched by dropwise addition of methanol (200 mL). To the stirred slurry maintained at 0 °C was added 1:1 (v/v) glacial acetic acid/10 M hydrochloric acid until the pH of 2−3 was reached. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C for 16 h. The mixture was neutralized by dropwise addition of methanolic potassium hydroxide (4 M) at 0 °C and then evaporated under reduced pressure. The residue was dissolved in water (150 mL) and continuously extracted with 4:1 chloroform/tetrahydrofuran over 80 h. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was evaporated. The residue was adsorbed onto neutral alumina, and the impregnated dispersion was applied to the top of a prepacked column of silica gel and eluted with 1:4 methanol/chloroform. The appropriate fractions were combined, filtered through a glass wool plug, and evaporated to give **3a** (4.64 g, 47%) as a light brown powder (mp 52−56 °C). An analytical sample was obtained by recrystallization from acetone by the slow diffusion of *n*-hexane vapors at 5−6 °C, giving **3a** as lustrous, white plates: mp 61.5−62 °C; $[\alpha]_D^{30}$ +14.8 (*c* 1.3, chloroform); IR ν_{max} (KBr) 3345, 2915, 2850, 1465 cm^{-1}; ^1H NMR δ 4.10 (2H, t, J = 5.0 Hz), 2.9 (2H, br s), 2.97 (2H, dd, J = 6.2, 3.5 Hz), 2.48 (2H, dd, J = 8.5, 3.5 Hz), 2.45 (2H, m), 1.48 (2H, t, J = 7.5 Hz), 1.29 (10H, m), 0.87 (3H, t, J = 7.5 Hz); ^{13}C NMR δ 78.6, 60.6, 56.3, 31.9, 29.5, 29.3, 28.3, 27.6, 22.7, 14.1; LRMS−FAB *m/e* (rel intensity %; positive *m*-$NO_2C_6H_5CO_2H$ MATRIX) 216 ($[M + H]^+$, 100), 198 (3), 154 (5), 142 (10),116 (26), 58 (15); HRMS−FAB calcd for $C_{12}H_{26}NO_2$ [M + H]$^+$ 216.1964, found 216.1980.

(3*S*,4*S*)-1-(4-Iodophenyl)pyrrolidine-3,4-diol (3d). To a stirred suspension of (3*R*,4*R*)-1,4-diiodobutane-1,4-diol (**7**)[41] (2.0 g, 5.9 mmol), potassium carbonate (1.46 g, 14.6 mmol), and 18-crown-6 (154 mg, 0.59 mmol) in dry DMF (30 mL) at 20 °C was added 4-iodoaniline (1.28 g, 5.85 mmol) in portions. The mixture was heated to 90 °C, and stirring was continued

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at 90 °C under an atmosphere of dry nitrogen for 9 days. The mixture was quenched by the addition of aqueous lithium chloride (45 mL, 2.0 M), and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over $MgSO_4$. The solution was filtered through a sintered glass funnel, and the filtrate was adsorbed onto neutral alumina by evaporation. The impregnated dispersion was applied to the top of a prepacked column and purified by flash chromatography over silica gel (9:1 diethyl ether/40−60 °C petroleum ether). The appropriate fractions were combined and filtered through a glass wool plug, and the eluent was evaporated under reduced pressure to give **3d** (0.60 g, 34%) as a pink solid (mp 129−131 °C). An analytical sample was obtained by recrystallization from ethyl acetate as light purple prisms: mp 134.5−135 °C; $[\alpha]_D^{31}$ +59.4 (*c* 0.4, acetone); IR ν_{max} (KBr) 3210, 2880, 2850, 1590, 1490 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.38 (2H, J = 9.0 Hz), 6.34 (2H, J = 9.0 Hz), 5.03 (2H, d, J = 3.5 Hz), 4.03 (2H, br s), 3.30 (4H, m); LRMS−FAB *m/e* (rel intensity %; positive *m*-$NO_2C_6H_5CO_2H$ MATRIX) 305 ($[M + H]^+$, 100), 304 (42), 289 (23), 232 (18), 176 (33), 165 (38). HRMS−FAB calcd for $C_{10}H_{14}NO_2I$ $[M + H]^+$ 304.9913, found 304.9913. Anal. Calcd for $C_{10}H_{12}NO_2I$: C, 39.36; H, 3.96; N, 4.59. Found: C, 39.61; H, 3.88; N, 4.33.

(3*S*,4*S*)-1-(2-Benzyloxyethyl)pyrrolidine-3,4-diol (3f). To a stirred suspension of (3*S*,4*S*)-1-(2-benzyloxyethyl)-3,4-bis-(methoxymethyloxy)pyrrolidine (**10b**) (5.0 g, 15.4 mmol) in methanol (13 mL) at 0 °C under an atmosphere of nitrogen was added dropwise 10 M hydrochloric acid (13 mL) using a pressure-equalizing addition funnel. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of nitrogen for 16 h. Volatile material was removed under reduced pressure, and the residue was basified by addition of *N*,*N*-dimethylethylamine (***Caution**: exothermic*) at −20 °C under an atmosphere of nitrogen with stirring. This mixture was allowed to warm slowly to 20 °C and stirred at that temperature for 2 h under an atmosphere of nitrogen. The volatile materials were removed under vacuum, and the residue was dissolved in saturated aqueous ammonium chloride (30 mL). The suspension was continuously extracted with ethyl acetate under an atmosphere of nitrogen for 16 h. The organic layer was collected and concentrated to approximately one-half of its original volume, to which an equal volume of 1,4-dioxane was added, and the extraction continued for an additional 80 h. The organic layers were dried over Na_2SO_4 and filtered through a sintered glass funnel, and the filtrate was adsorbed onto neutral alumina by evaporation. The impregnated dispersion was applied to the top of a prepacked column and purified by flash chromatography over silica gel (1:9 methanol/chloroform). The appropriate fractions were combined and filtered through a glass wool plug, and the eluent was evaporated under reduced pressure to give **3f** (2.52 g, 69%) as a pale yellow oil. An analytical sample was obtained by preparative silica plate thin-layer chromatography (two-plate elutions with 1:19 methanol/chloroform). The appropriate band was excised and extracted with methanol and filtered through a sintered glass microfunnel, and the filtrate was evaporated under reduced pressure. The residue was redissolved in chloroform. This solution was filtered through a fluted paper, and the filtrate was evaporated to give **3f** as a clear oil: $[\alpha]_D^{30}$ −5.05 (*c* 4.01, chloroform); IR ν_{max} (film) 3355, 2920, 2870, 1620 cm^{-1}; ^1H NMR δ 7.40−7.20 (5H, m), 5.30 (2H, s br), 4.52 (2H, s br), 4.47 (2H, s br), 3.80 (2H, m), 3.68 (2H, m), 3.40 (4H, m); ^{13}C NMR δ 137.1, 128.7, 128.2, 74.7, 73.5, 65.0, 60.5, 57.5; LRMS−EI *m/e* (rel intensity %) 237 (M^+, 0.1), 208 (10), 164 (120), 116 (73), 91 (100), 65 (12). HRMS−EI calcd for $C_{13}H_{19}NO_3$ (M^+) 237.1365, found 237.1368.

(3*S*,4*S*)-1-*n*-Octyl-3,4-bis(trifluoromethanesulfonyloxy)-pyrrolidine (4a). General Procedure C. To a stirred suspension of (3*S*,4*S*)-1-*n*-octylpyrrolidine-3,4-diol (**3a**) (1.00 g, 4.65 mmol) and triethylamine (0.99 g, 9.8 mmol) in 65 mL of anhydrous, degassed dichloromethane at −85 °C under an atmosphere of dry nitrogen was added dropwise a solution of trifluoromethanesulfonic anhydride (2.62 g, 9.30 mmol) in 40 mL of dry, degassed dichloromethane using a double-tipped needle of stainless steel. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for 16 h. The mixture was quenched by addition of saturated aqueous sodium hydrogen carbonate (35 mL), and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried over Na_2SO_4. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated at 0 °C under reduced pressure (1.0−1.5 mmHg). The residue was adsorbed onto neutral alumina, and the impregnated dispersion was applied to the top of a prepacked column of silica gel and eluted with 1:49 ethyl acetate/40−60 °C petroleum ether. The appropriate fractions were combined, filtered through a glass wool plug, and evaporated to give **4a** (0.67 g, 30%) as a clear gel. An analytical sample was obtained by preparative silica plate thin-layer chromatography (two-plate elutions with 40−60 °C petroleum ether at a refrigerated temperature of 5 °C in the dark). The appropriate band was excised and extracted with methanol and filtered through a sintered glass microfunnel. The filtrate was evaporated under reduced pressure, and the residue was redissolved in chloroform. This solution was filtered through a fluted paper, and the filtrate was evaporated to give **4a** as plates: mp 35−40 °C; $[\alpha]_D^{30}$ +40.9 (*c* 0.98, chloroform); IR ν_{max} (KBr) 2930, 1435, 1310, 1190 cm^{-1}; ^1H NMR δ 5.35 (2H, t, J = 4.9 Hz), 3.19 (2H, dd, J = 10.2, 5.5 Hz), 2.86 (2H, dd, J = 10.0, 4.0 Hz), 2.49 (2H, m), 1.48 (2H, m), 1.29 (10H, m), 0.91 (3H, t, J = 6.0 Hz); ^{13}C NMR δ 118.7 (q, J_{CF} = 315.4 Hz), 87.9, 57.7, 55.0, 31.8, 29.4, 29.2, 27.8, 27.2, 22.7, 14.1; ^{19}F NMR δ −79.0 (s); LRMS−EI *m/e* (rel intensity %) 479 (M^+, 2.9), 379 (100), 180 (3.8), 80 (18.3), 41 (14.2). HRMS−EI calcd for $C_{14}H_{23}F_6NO_6S_2$ (M^+) 479.0871, found 479.0878.

(3*R*,4*R*)-1-*n*-Octyl-3,4-difluoropyrrolidine (5a). General Procedure D. To a stirred solution of (3*S*,4*S*)-3,4-bis(trifluoromethanesulfonyloxy)pyrrolidine (**4a**) (0.64 g, 1.34 mmol) in anhydrous THF (10 mL) at −85 °C under an atmosphere of dry nitrogen was added dropwise a solution of tetra-*n*-butylammonium fluoride (4.02 mL, 4.02 mmol, 1 M) in dry THF (15 mL) by means of a stainless steel, double-tipped needle. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for 16 h. The mixture was quenched by addition of saturated aqueous sodium hydrogen carbonate (35 mL), and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (2 × 20 mL) and dried over Na_2SO_4. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated at 0 °C under reduced pressure (1.0−1.5 mmHg). The residue was adsorbed onto neutral alumina, and the impregnated dispersion was applied to the top of a prepacked column of silica gel and eluted with 1:49 ethyl acetate/40−60 °C petroleum ether. The appropriate fractions were combined, filtered through a glass wool plug, and evaporated to give **5a** (0.24 g, 83%) as a clear, viscous oil. An analytical sample was obtained by preparative silica plate thin-layer chromatography and three-plate elutions with *n*-hexane at a refrigerated temperature of 5 °C in the dark. The appropriate band was excised and extracted with methanol and filtered through a sintered glass microfunnel. The filtrate was evaporated under reduced pressure, and the residue was redissolved in chloroform. This solution was filtered through a fluted paper, and the filtrate was evaporated to give **5a** as a soft gel: $[\alpha]_D^{30}$ −20.0 (*c* 1.23, chloroform); IR ν_{max} (KBr) 2930, 1440 cm^{-1}; ^1H NMR δ 5.15 (2H, dddd, $^2J_{HF}$ = 53.2 Hz, $^3J_{HF}$ = 16.3 Hz, $^3J_{HH}$ = 5.1, 3.0 Hz), 3.14 (2H, m), 2.88 (2H, ddd, $^3J_{HF-trans}$ = 24.0 Hz, $^2J_{HH}$ = 11.5, $^3J_{HH}$ = 3.0 Hz), 2.57 (2H, m), 1.70−1.25 (12H, m), 0.88 (3H, t, J = 6.9 Hz); ^{13}C NMR δ 95.0 (dd, $^1J_{CF}$ 181.5 Hz, $^2J_{CF}$ = 30.0 Hz), 58.0 (d, $^2J_{CF}$ = 26.0 Hz), 56.4, 31.8, 29.6, 27.6, 24.0, 22.7, 19.7, 13.8; ^{19}F NMR δ −186.4; LRMS−FAB *m/e* (rel

intensity %; positive *m*-$NO_2C_6H_5CO_2H$ MATRIX) 220 ([M + H]$^+$, 100), 184 (13), 142 (33), 120 (26); HRMS−FAB calcd for $C_{12}H_{24}F_2N$ (M^+) 220.1890, found 220.1877.

(3*R*,4*R*)-1-[1,1′-Biphenyl-4-yl]-3,4-difluoropyrrolidine (5e). A thick-walled tube equipped with a gas outlet, a septum, and a magnetic stirring bar was charged with (3*R*,4*R*)-1-(4-iodophenyl)-3,4-difluoropyrrolidine (**5d**) (25 mg, 0.08 mmol), phenylboronic acid (10 mg, 0.09 mmol), potassium carbonate (28 mg, 0.02 mmol), and 1:1 acetone/distilled water (3.0 mL) and maintained at 0 °C with stirring under an atmosphere of dry nitrogen. The apparatus was purged with nitrogen, and three successive freeze−pump−thaw cycles were performed at −10 °C with stirring. A solution of palladium(II) acetate in benzene (0.1 mL, 0.045 M) was added via a syringe. Following two additional freeze−pump−thaw cycles, the vessel was charged with nitrogen and maintained at 60 °C with stirring for 16 h. Upon cooling, the mixture was filtered and the filtrate was evaporated. The residue was purified by preparative silica plate thin-layer chromatography (three-plate elutions with *n*-hexane at a refrigerated temperature of 5 °C in the dark). The appropriate band was excised and extracted with methanol and filtered through a sintered glass microfunnel. The filtrate was evaporated under reduced pressure, and the residue was redissolved in chloroform. This solution was filtered through a fluted paper, and the filtrate was evaporated to give **5e** (5.0 mg, 24%) as a gray, semicrystalline material: $[\alpha]_D^{32}$ −23.4 (*c* 0.2, chloroform); IR ν_{max} (film) 2850, 1610, 1530, 1490 cm^{-1}; ^{1}H NMR δ 7.55 (4H, m), 7.42 (2H, t, J = 7.5 Hz), 7.27 (1H, t, J = 6.2 Hz), 6.68 (2H, d, J = 9.5 Hz), 5.31 (2H, ddm, $^3J_{HF}$ = 49.6, $^2J_{HH}$ = 11.0 Hz), 3.80 (2H, m), 3.66 (2H, m); ^{13}C NMR δ_C 146.2, 141.2, 130.0, 128.8, 128.1, 126.4, 126.2, 112.3, 92.7 (dd, $^1J_{CF}$ = 179.8 Hz, $^2J_{CF}$ = 33.0), 51.8 (dd, $^2J_{CF}$ = 22.0 Hz, $^3J_{CF}$ = 5.9); LRMS−FAB *m/e* (rel intensity %; positive *m*-$NO_2C_6H_5CO_2H$ MATRIX) 259 (M^+, 40), 242 (16), 185 (17), 154 (22), 137 (23), 115 (100); HRMS−FAB calcd for $C_{16}H_{15}F_2N$ (M^+) 259.1173, found 259.1160.

(3*R*,4*R*)-1-(2-Hydroxyethyl)-3,4-difluoropyrrolidine (5g). To a stirred solution of (3*S*,4*S*)-1-(2-benzyloxyethyl)-3,4-difluoropyrrolidine **5f** (0.332 g, 1.38 mmol) in dry dichloromethane (6 mL) at −85 °C under an atmosphere of dry nitrogen was added via a syringe a boron trichloride/dimethyl sulfide complex[44] (1.38 mL, 2.76 mmol, 2.0 M) in dichloromethane. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for 4 h. The mixture was quenched by the addition of neat *N*,*N*-dimethylethylamine (1 mL) (the standard literature procedure[44] employing a saturated sodium hydrogen carbonate quench did not liberate the pyrrolidine), and digestion was continued at this temperature under an atmosphere of dry nitrogen for an additional 1 h. Saturated aqueous ammonium chloride (5 mL) was then added, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL) and then with THF (10 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried over Na_2SO_4. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated. The residue was purified by flash column chromatography on silica gel eluted with 1:32 methanol/chloroform precooled to 5 °C. The appropriate fractions were combined, filtered through a glass wool plug, and evaporated to give **5g** (137 mg, 66%) as a clear oil. An analytical sample was obtained by preparative silica plate thin-layer chromatography (two-plate elutions with 2:1 chloroform/diethyl ether at a refrigerated temperature of 5 °C in the dark). The appropriate band was excised and extracted with methanol and filtered through a sintered glass microfunnel. The filtrate was evaporated under reduced pressure, and the residue was redissolved in chloroform. This solution was filtered through a fluted paper, and the filtrate was evaporated to give **5g** as a colorless gel, which upon standing gradually became a waxy solid: mp between 15 and 25 °C; $[\alpha]_D^{30}$ −24.3 (*c* 0.48, chloroform); IR ν_{max} (film) 3360, 2930, 2860, 2815, 1454 cm^{-1}; ^{1}H NMR δ 5.13 (2H, dddd, $^2J_{HF}$ = 52.2 Hz, $^3J_{HF}$ =17.9 Hz, $^3J_{HH}$ = 5.5, 3.5 Hz), 3.64 (2H, t, J = 6.0 Hz), 3.12 (2H, ddd, $^3J_{HF}$ = 27.5 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 5.5 Hz), 2.86 (2H, ddd, $^3J_{HF}$ = 25.2 Hz, $^2J_{HH}$ = 11.0 Hz, $^3J_{HH}$ = 3.5 Hz), 2.73 (2H, m), 1.60 (1H, br); ^{13}C NMR (150 MHz) δ 95.3 (dd, $^1J_{CF}$ = 180.8 Hz, $^2J_{CF}$ = 29.7 Hz), 59.6, 57.8 (dd, $^2J_{CF}$ = 22.0 Hz, $^3J_{CF}$ = 5.7 Hz), 57.1; ^{19}F NMR (565 MHz) δ −183.9 (m); LRMS−EI *m/e* (rel intensity %) 151 (M^+, 5), 120 (100), 100 (5), 73 (5), 41 (7). HRMS−EI calcd for $C_6H_{11}F_2NO$ (M^+) 151.0809, found 151.0810.

(2*R*,3*R*)-1,4-Diodobutane-2,3-diol (7). A previous account did not give experimental details.[41] To a stirred solution of (4*S*,5*S*)-4,5-diiodomethyl-2,2-dimethyl-1,3-dioxolane[43] (15.0 g, 39.4 mmol) in THF (25 mL) at 0 °C under an atmosphere of dry nitrogen was added dropwise a solution of 4:1 trifluoroacetic acid/methanol by means of a pressure-equalizing addition funnel. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of nitrogen for 24 h. The mixture was quenched by addition of water (20 mL), and the aqueous layer was extracted with ethyl acetate (3 × 35 mL). The combined organic layers were washed with brine (2 × 35 mL) and dried over Na_2SO_4. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated at 0 °C under reduced pressure (1.0−1.5 mmHg). The residue was adsorbed onto neutral alumina, and the impregnated dispersion was applied to the top of a prepacked column of silica gel and eluted with 1:4 ethyl acetate/40−60 °C petroleum ether. The appropriate fractions were combined, filtered through a glass wool plug, and evaporated to give **7** (4.83 g, 36%) as a yellow solid (mp 110−115 °C). An analytical sample was obtained by recrystallization from chloroform, giving **7** as needles: mp 114.5−115 °C; $[\alpha]_D^{34}$ +9.6 (*c* 1.0, methanol); IR ν_{max} (Nujol) 3215, 1460 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.25 (2H, d, J = 7.4 Hz), 3.75 (2H, m), 3.24 (2H, m); LRMS−FAB *m/e* (%) 341 (M^+, 15), 325 (23), 281 (42), 267 (24), 221 (40), 207 (54), 193 (28).

(2*S*,3*S*)-2,3-Bis(methoxymethyloxy)-4-methylsulfonyloxybutylmethanesulfonate (9). To a stirred solution of (2*S*,3*S*)-2,3-bis(methoxymethyloxy)butane-1,4-diol (**8**) (15.0 g, 71.4 mmol) and triethylamine (18.1 g, 179 mmol) in dry dichloromethane (200 mL) at 0 °C under an atmosphere of dry nitrogen was added dropwise a solution of methanesulfonyl chloride (20.5 g, 179 mol) in dry dichloromethane (45 mL) by means of a stainless steel, double-tipped needle. The mixture was maintained at 0 °C with stirring under an atmosphere of dry nitrogen for 1 h. The mixture was quenched by addition of water (50 mL), and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed sequentially with water (50 mL), hydrochloric acid (50 mL, 4 M), saturated aqueous sodium hydrogen carbonate (50 mL), and brine (2 × 50 mL) and then dried over $MgSO_4$. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated. The residue was adsorbed onto neutral alumina, and the impregnated dispersion was applied to the top of a prepacked column of silica gel and eluted with 1:1 ethyl acetate/40−60 °C petroleum ether. The appropriate fractions were combined, filtered through a glass wool plug, and evaporated to give **7** (12.8 g, 49%) as a pale yellow oil. An analytical sample was obtained by recrystallization from chloroform at −35 °C, giving **9** as needles: mp 89.5−90 °C; $[\alpha]_D^{27}$ +10.4 (*c* 0.25, chloroform); IR ν_{max} (KBr) 2940, 2900, 1350 cm^{-1}; ^{1}H NMR δ 4.72 (4H, d, J = 3.0 Hz, OCH_2O), 4.41 (2H, dd, J = 4.00 Hz), 4.30 (2H, dd, J = 4.5 Hz), 4.02 (2H, t, J = 3.0 Hz, CH), 3.38 (6H, s), 3.04 (6H, s); ^{13}C NMR δ_C 97.4, 75.0, 68.0, 56.2, 37.5; LRMS−EI *m/e* (rel intensity %) 289 [$C_7H_{13}O_8S_2$, (M^+ − $C_3H_9O_2$), (3)], 289 (4), 185 (5), 151 (8), 98 (7), 85 (47), 45 (100). HRMS−EI calcd for $C_7H_{13}O_8S_2$ (M^+ − $C_3H_9O_2$) 289.0052, found 289.0038.

(3*S*,4*S*)-1-(2-Hydroxyethyl)-3,4-bis(methoxymethyloxy)pyrrolidine (10a). To a stirred suspension of (2*S*,3*S*)-2,3-bis(methoxymethyloxy)-4-methylsulfonyloxybutylmethane-

(44) Scheurer, A.; Mosset, P.; Saalfrank, R. W. *Tetrahedron: Asymmetry* **1997**, *8*, 1243−1251.

sulfonate (**9**) (13.0 g, 35.5 mmol), potassium carbonate (14.7 g, 107 mmol), 18-crown-6 (0.89 g, 3.5 mmol), and potassium iodide (0.59 g, 3.55 mmol) in dry DMF (120 mL) at −10 °C under an atmosphere of dry nitrogen was added via a syringe a solution of ethanolamine (2.14 mL, 2.16 g, 35.5 mmol) in dry triethylamine (3 mL). The mixture was heated slowly to 100 °C and stirred at that temperature for 48 h under an atmosphere of dry nitrogen. The DMF was removed by distillation under reduced pressure, and the residue was suspended in saturated aqueous ammonium chloride (150 mL) and continuously extracted for 80 h with 3:1 ethyl acetate/butanone. The organic layer was dried over K_2CO_3 and filtered through a sintered glass funnel, and the filtrate was evaporated. The gummy residue was purified by short-path distillation (bp 190−196 °C/1.2 mmHg) to give a glassy solid that was adsorbed onto neutral alumina, and the impregnated dispersion was applied to the top of a prepacked column of silica gel and eluted with 49:1 chloroform/methanol. The appropriate fractions were combined, filtered through a glass wool plug, and evaporated to give **10a** (4.76 g, 57%) as a yellow gum. An analytical sample was obtained by preparative silica plate thin-layer chromatography (two-plate elutions with chloroform). The appropriate band was excised and extracted with methanol and filtered through a sintered glass microfunnel. The filtrate was evaporated under reduced pressure, and the residue was redissolved in chloroform. This solution was filtered through a fluted paper, and the filtrate was evaporated to give **10a** as a clear viscous oil: $[\alpha]_D^{31}$ −0.8 (*c* 0.51, methanol); IR ν_{max} (film) 3420, 2940, 2890 cm^{-1}; ^{1}H NMR δ_H 4.64 (2H, d, J = 7.5 Hz), 4.58 (2H, d, J = 7.5 Hz), 4.07 (2H, J = 4.0 Hz), 3.56 (2H, t, J = 5.5 Hz), 3.30 (6H, s), 2.92 (2H, dd, J = 10.0, 7.0 Hz), 2.70 (1H, br), 2.60 (2H, m), 2.50 (2H, dd, $^3J_{HH}$ = 11.0, 5.2 Hz); ^{13}C NMR δ_C 95.8, 81.5, 59.7, 58.7, 57.8, 55.5; LRMS−EI *m/e* (rel intensity %) 235 (M^+, 1.1), 206 (10), 204 (100), 160 (4), 86 (5), 45 (65); HRMS−EI calcd for $C_{10}H_{21}NO_5$ (M^+) 235.1420, found 235.1420.

(3*S*,4*S*)-1-(2-Benzyloxyethyl)-3,4-bis(methoxymethoxy-)pyrrolidine (10b). To a stirred suspension of (3*S*,4*S*)-1-(2-hydroxyethyl)-3,4-bis(methoxymethyloxy)pyrrolidine (**10a**) (4.50 g, 19.1 mmol) and sodium hydride (0.88 g, 38.3 mmol, rinsed with *n*-hexane) in dry tetrahydrofuran (150 mL) at 20 °C under an atmosphere of dry nitrogen was added via syringe benzyl bromide (3.59 g, 4.48 mL, 21.0 mmol). The mixture was slowly brought to reflux, and stirring was continued for 3 h under an atmosphere of dry nitrogen. Saturated aqueous ammonium chloride (40 mL) was then added, and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over K_2CO_3. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated. The residue was purified by flash column chromatography on silica gel with gradient elution using methanol/chloroform ranging from 0:100 to 1:49. The appropriate fractions were combined, filtered through a glass wool plug, and evaporated to give **10b** (5.2 g, 82%) as a colorless oil. An analytical sample was obtained by preparative silica plate thin-layer chromatography (two-plate elutions with chloroform). The appropriate band was excised and extracted with methanol and filtered through a sintered glass microfunnel. The filtrate was evaporated under reduced pressure, and the residue was redissolved in chloroform. This solution was filtered through a fluted paper, and the filtrate was evaporated to give **10b** as a clear oil: $[\alpha]_D^{30}$ +5.05 (*c* 4.36, chloroform); IR ν_{max} (film) 2890, 2820, 1670 cm^{-1}; ^{1}H NMR δ 7.31 (5H, m), 4.70 (2H, d, J = 6.5 Hz), 4.62 (2H, d, J = 6.5 Hz), 4.52 (2H, s), 4.13 (2H, t, J = 4.9 Hz), 3.61 (2H, t, J = 5.5 Hz), 3.36 (6H, s), 3.00 (2H, dd, J = 10.0, 6.0 Hz), 2.70 (2H, m), 2.63 (2H, dd, J = 10.0, 5.0 Hz); ^{13}C NMR δ 138.4, 128.4, 127.7, 127.6, 95.7, 81.5, 73.1, 69.0, 59.4, 55.5, 55.4; LRMS−EI *m/e* (rel intensity %) 173 (15), 111 (20), 91 (100); LRMS−FAB *m/e* (rel intensity %; positive *m*-$NO_2C_6H_5CO_2H$ MATRIX) 326 ([M + H]$^+$, 100), 324 (43), 294 (15), 264 (8), 218 (21), 204 (72); HRMS−FAB calcd for $C_{17}H_{28}NO_5$ [M + H]$^+$ 326.1967, found 326.1962.

Catalytic Asymmetric Ethylation of Benzaldehyde to Give 1-(*R*)-Phenylpropanol (11b).[45] **Representative procedure** (5 mol % catalyst **5g** at −20 °C to 20 °C). To a stirred solution of benzaldehyde (160 mg, 1.52 mmol) and (3*S*,4*S*)-1-(2-hydroxyethyl)-3,4-difluoropyrrolidine (**5g**) (12 mg, 0.08 mmol) in 2.0 mL of anhydrous toluene at −20 °C under an atmosphere of dry nitrogen was injected a solution of diethylzinc (1.64 mL, 1.81 mmol, 1.1 M in toluene). The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for 16 h. The mixture was allowed to warm slowly to 20 °C, and stirring was continued for 3 h at 20 °C under an atmosphere of dry nitrogen. Progress of the reaction was monitored by thin-layer chromatography (plate treated with potassium permanganate solution and then heated). The mixture was quenched with hydrochloric acid (5 mL, 5 M). The aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried over $MgSO_4$. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography over silica gel (1:9 ethyl acetate/40−60 °C petroleum ether). The appropriate fractions were combined and filtered through a glass wool plug, and the eluent was evaporated under reduced pressure to give **11b** as a pale yellow oil (168 mg, 82%). A sample for HPLC analysis (see following description for conditions) was obtained from Kugelrohr bulb-to-bulb distillation (123 mg, 60%): bp 94−95 °C; $[\alpha]_D^{36}$ +9.3 (*c* 1.80, chloroform), (lit.[45] $[\alpha]^{22}_D$ −48.6 (*c* 5.13, chloroform) for the (*S*)-enantiomer); IR ν_{max} (film) 3365, 2970, 2870, 1600 cm^{-1}; ^{1}H NMR δ 7.37 (5H, m), 4.54 (1H, t, J = 6.0 Hz), 2.93 (1H, br s), 1.78 (2H, m), 0.92 (3H, t, J = 7.5 Hz); ^{13}C NMR δ 144.8, 128.4, 127.4, 126.2, 75.9, 31.9, 10.2.

Conditions for HPLC analysis: stationary phase, Daicel chiralcel OD column (250 × 4.6 mm), recorded on a Shimadzu SPD-10A VP instrument, 254 nm detection wavelength, isocratic at 20 °C, mobile phase of doubly redistilled propan-2-ol/*n*-hexane (1:49, v/v), and 0.5 mL/min flow rate. Found: *R*-isomer, t_R = 32.5 min; *S*-isomer, t_R = 39.7 min.

Catalytic Asymmetric Epoxidation of Geraniol to Give (2*R*,3*R*)-Epoxygeraniol (13b).[35] **Representative procedure** (10 mol % catalyst **5a** at −20 °C to 20 °C). To a stirred solution of titanium tetraisopropoxide (69 mg, 0.07 mL, 0.24 mmol), geraniol (**12**) (250 mg, 0.28 mL, 1.62 mmol), and (3*R*,4*R*)-3,4-difluoro-1-octylpyrrolidine (**5a**) (35 mg, 0.16 mmol, 10 mol %) in dry dichloromethane (0.5 mL) at −20 °C under an atmosphere of dry nitrogen was added a solution of *tert*-butyl hydroperoxide (6.08 M, 0.4 mL) in dry dichloromethane via a syringe. The mixture was allowed to warm slowly to 20 °C, and stirring was continued at 20 °C under an atmosphere of dry nitrogen for 12 h. Progress of the reaction was monitored by thin-layer chromatography (plate treated with anisaldehyde solution and then heated). The mixture was quenched by the addition of aqueous acidified iron(II) sulfate (10 mL),[35] and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over Na_2SO_4. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated under reduced pressure. This product was purified by flash column chromatography over silica gel (20:80 ethyl acetate/40−60 °C petroleum ether). The appropriate fractions were combined and filtered through a glass wool plug, and the eluent was evaporated under reduced pressure to give **13b** (0.247 g, 90%) as a mobile oil: $[\alpha]_D^{31}$ +2.74 (*c* 1.75, chloroform); IR ν_{max} (film) 3400, 2900, 2870, 1680 cm^{-1}; ^{1}H NMR δ 5.10 (1H, t, J = 6.0 Hz), 3.82 (1H, dd, J = 12.0, 5.0 Hz), 3.67 (1H, dd, J = 12.0, 6.0 Hz), 2.99 (1H, t, J = 5.0 Hz), 2.60 (1H, br),

(45) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657−1660.

2.08 (2H, t, J = 8.0 Hz), 1.68 (3H, s), 1.62 (3H, s), 1.49 (2H, m), 1.30 (3H, s); ^{13}C NMR δ 132.1, 123.4, 63.2, 61.4, 61.2, 38.5, 25.7, 23.7, 17.6, 16.8; LRMS−FAB *m/e* (rel intensity %; positive *m*-$NO_2C_6H_5CO_2H$ MATRIX) 193 ($[M + Na]^+$, 65), 171 (26), 153 (58), 139 (17), 135 (50), 123 (49), 119 (11), 109 (100). HRMS−FAB calcd for $C_{10}H_{18}NaO_2$ $[M + Na]^+$ 193.1204, found 193.1220.

(2*R*,3*R*)-1-Acetoxyepoxygeraniol.[35] To a stirred solution of (2*R*,3*R*)-epoxygeraniol (100 mg, 0.65 mmol) and pyridine (94 mg, 0.78 mmol) in anhydrous dichloromethane (5 mL) at 0 °C under an atmosphere of dry nitrogen was added a solution of acetic anhydride (144 mg, 0.14 mL, 158 mmol) in dichloromethane (1 mL) via a syringe. The mixture was allowed to warm slowly to 20 °C, and stirring was continued for 3 h at 20 °C under an atmosphere of dry nitrogen. Progress of the reaction was monitored by thin-layer chromatography (plate treated with cerium(IV) sulfate solution and then heated). The mixture was quenched by the addition of saturated aqueous sodium carbonate (15 mL) and transferred to a separating funnel. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried over $MgSO_4$. The solution was filtered through a sintered glass funnel, and the filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography over silica gel (1:55 ethyl acetate/40−60 °C petroleum ether). The appropriate fractions were combined and filtered through a glass wool plug, and the eluent was evaporated under reduced pressure to give (2*R*,3*R*)-1-acetoxyepoxygeraniol (115 mg, 92%) as a clear oil: $[\alpha]_D^{27}$ +21.1 (*c* 3.0, chloroform); IR ν_{max} (film) 2965, 2930, 2856, 1745, 1630 cm^{-1}; ^{1}H NMR δ 5.08 (1H, dt, J = 7.5, 1.5 Hz), 4.32 (1H, dd, J = 12.0, 5.0 Hz), 4.05 (1H, dd, J = 11.5, 6.5 Hz), 2.99 (1H, J = 7.5, 5.0 Hz), 2.11 (3H, s), 2.08 (2H, q, J = 5.5 Hz), 1.68 (3H, s), 1.63 (3H, s), 1.48 (2H, m), 1.31 (3H, s); ^{13}C NMR δ_C 170.8, 132.2, 123.3, 63.4, 60.5, 59.7, 38.3, 25.7, 23.6, 20.7, 17.6, 16.9.

^{1}H NMR shift analysis[35] of (2*R*,3*R*)-1-acetoxyepoxygeraniol: 10 mg (0.05 mmol) in C_6D_6 (0.5 mL) was treated with consecutive portions of 10−20 μL of a filtered solution of 35 mg of europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] and Eu(hfc)$_3$ in 0.5 mL of C_6D_6. The acetate signal was measured by quantitative integration at 250 MHz.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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