Enantiospecific and Stereoselective Synthesis of Polyhydroxylated Pyrrolidines and Indolizidines from *trans*-4-Hydroxy-L-proline

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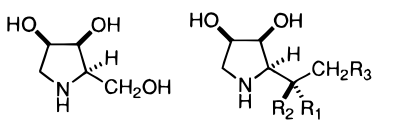
Received March 1, 1996[⊗]

We have developed a short, efficient, and stereoselective synthesis of polyhydroxylated pyrrolidine and indolizidine glycosidase inhibitors starting from 4-hydroxy-L-proline. The regio- and stereoselective hydroxylation of an *N*-Pf-4-oxoproline enolate and the stereoselective reduction of the resulting keto alcohol allowed us to introduce the *cis* diol present in the target compounds. The different side chains needed to complete the syntheses of the target compounds were introduced by reduction of the ester group of a substituted proline or by reaction of organolithium or organomagnesium reagents with the same group followed by stereoselective reduction of the resulting ketones. Hydrogenolysis of the alcohols thus obtained gave the hydrochlorides of the desired pyrrolidine glycosidase inhibitors, which were obtained in nine steps in overall yields greater than 50%. The indolizidine glycosidase inhibitor 8-*epi*-swainsonine was also prepared using this approach.

Introduction

The outer envelopes of cells are charged with glycoproteins, which are vital for normal cell−cell communication. Several types of enzymes are responsible for the processing of the glycoside portions of glycoproteins; among them the glycosidases play a key function.[1] Polyhydroxylated pyrrolidines and indolizidines have attracted a great deal of interest due to their ability to inhibit glycosidases and glycoprotein processing;[2] for instance, pyrrolidines **2**−**4a** and indolizidine **5a** (swainsonine) are potent inhibitors of α-mannosidases,[3] while triol **1** strongly inhibits α-galactosidase.[4] Glycosidase inhibitors have potential therapeutic value as anticancer and antiviral agents; in particular, mannosidase inhibitors have been proposed as anti-HIV agents.[5]

The potentially useful biological activities exhibited by polyhydroxylated pyrrolidines and indolizidines have prompted extensive efforts toward their syntheses, and numerous approaches to these kinds of compounds have been reported.[2] Fleet and co-workers have published several syntheses of enantiomerically pure **1**−**5** and their analogues, starting from carbohydrate precursors that already incorporate several of the hydroxyl groups, with the apropriate configurations, present in the target compounds. (*S*)-Glutamic acid,[6] (*S*)-serine,[7] and malic acid[8] have also served as chiral starting materials for the synthesis of **1**−**5**. Other approaches have made use of the Sharpless epoxidation to induce enantioselection in the preparation of **5a** and analogues of **2**−**4**.[9] Almost all of those approaches involve the use of sophisticated protecting group introduction and removal sequences, resulting in long syntheses and low overall yields. In addition, the use of starting materials with multiple chiral centers means that the syntheses usually lack flexibility, often being applicable to only one or two diastereomers of the target compound.



1 **2a**: R_1=H; R_2=R_3=OH **5a**: R_1=OH; R_2=H
2b: R_2=H; R_1=R_3=OH **5b**: R_1=H; R_2=OH
3a: R_1=R_3=H; R_2=OH
3b: R_2=R_3=H; R_1=OH
4a: R_1=H; R_2=OH; R_3=F
4b: R_1=OH; R_2=H; R_3=F

In this paper we present a flexible and efficient approach to enantiomerically pure compounds **1**−**5** from *trans*-4-hydroxyproline (**6**).

Results and Discussion

We envisioned hydroxyproline **6** as an ideal precursor to **1**−**5**: it already incorporates the required pyrrolidine ring; its 4-hydroxyl group should be amenable to oxidation to provide a 4-oxoproline (such as **7**),[10] which could,

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1996.

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(4) (a) Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127. (b) Austin, G. N.; Baird, P. D.; Fleet, G. W. J.; Peach, J. M.; Smith, P. W.; Watkin, D. J. *Tetrahedron* **1987**, *43*, 3095.

(5) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 6317, and references therein.

(6) (a) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1987**, *35*, 2140. (b) Ikota, N.; Hanaki, A. *Heterocycles* **1987**, *26*, 2369.

(7) Burley, I.; Hewson, A. T. *Tetrahedron Lett.* **1994**, *35*, 7099.

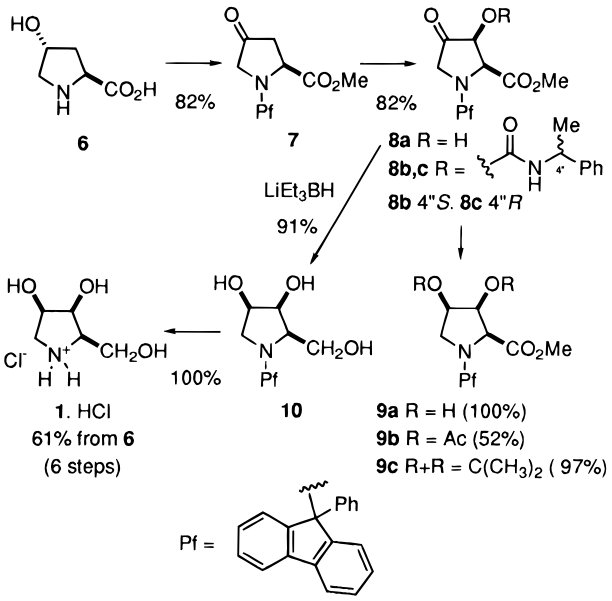
(8) Leeper, F. J.; Howard, S. *Tetrahedron Lett.* **1995**, *36*, 2335.

(9) (a) Jäger, V.; Hümmer, W. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1171. (b) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 420.

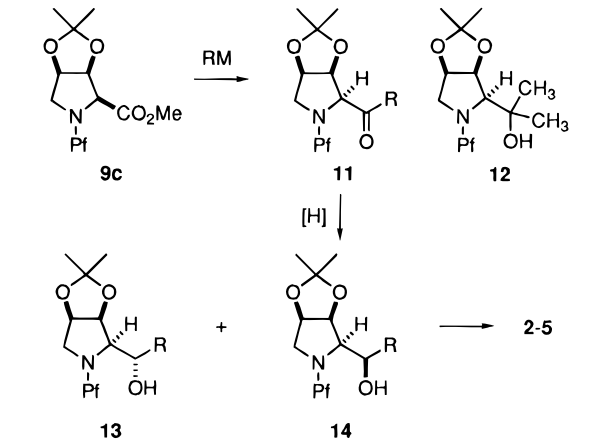
(10) In related syntheses of kainoids, 4-oxoprolines have been used for the introduction of carbon appendages at C-3 of the proline ring: (a) Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658. (b) Baldwin, J. E.; Rudolph, M. *Tetrahedron Lett.* **1994**, *33*, 6163. (c) Sharma, R.; Lubell, W. D. *J. Org. Chem.* **1996**, *61* , 202.

S0022-3263(96)00424-0 CCC: $12.00

Scheme 1



Scheme 2



a: R = CH_3
b: R = CH_2OMOM
c: R = $(CH_2)_2C(OCH_2)_2$
d: R = CH_2F

Ketone	[H]	Products (yield)
11a	$LiEt_3BH$	**13a** (100%)
11a	K-Selectr.®	**14a** (100%)
11b	$LiEt_3BH$	**14b** (100%)
11b	$NaBH_4$	**14b**/**13b**: 3/1 (95%)
11c	$LiEt_3BH$	**14c**/**13c**: 1/4 (92%)
11d	K-Selectr.®	**14d** (95%)
11d	$NaBH_4$	**14d**/**13d**: 2/1 (90%)

in turn, be manipulated to introduce the *cis*-3,4-diol moiety of the target compounds; and finally, it possesses a carboxymethyl group attached at C-2 that could be elongated to give the various side chains present in **1**−**5**.

Our approach to compounds **1**−**5** from **6** is shown in Schemes 1 and 2. We faced first the introduction of the 3-hydroxy group by hydroxylation of a suitably protected 4-oxoproline enolate. We chose the 9-phenylfluoren-9-yl as the *N*-protecting group since we expected that it would steer both the enolate formation (away from C-2 and C-5) and the selective hydroxylation (from the *Si* face, away from the phenyl ring).[11,12] In the event, treatment of prolinone **7**, prepared in three steps (82% yield) from *trans*-4-hydroxy-L-proline (**6**), with NaHMDS followed by oxidation of the resulting enolate with MoOPH led to ketoalcohol **8a** (82%) as a sole reaction product.[12,13] The configuration of the newly introduced chiral center was assigned by reduction of the 4-keto group of **8a** with $NaBH_4$ (quantitative) and acetylation of the resulting diol (**9a**) to give diacetate **9b** (52%); NOE experiments performed on **9b** showed that H2, H3, and H4 were all *syn* to each other, thus confirming the configurations depicted in Scheme 1.

The transformation of **8a** into **9a** allowed us to determine the configuration at C3 and also to demonstrate that the 4-keto group could be stereoselectively reduced (*anti* to the 3-hydroxy group) to provide the desired *cis* 3,4-diol system present in **1**−**5**.

Carbamoylation of **8a** with both (*S*)- and (*R*)-phenylethyl isocyanate (quantitative) allowed us to establish its enantiomeric purity. ^{1}H NMR analysis of the resulting diastereomeric carbamates **8b**,**c** showed that **8a** had a ratio of enantiomers (er) > 99.5/0.5, indicating that the hydroxylation conditions employed did not affect the chiral center of the *N*-Pf-oxoproline **7**.

Once we had secured a method to prepare the *all-cis*-3,4-dihydroxyproline **9a**, we turned our attention to the problem of introducing the appropriate side chains at C2. The simplest of our targets, α-galactosidase inhibitor **1**, should be easily accessible by reduction of either **8a** or **9a**, and, in fact, it was efficiently obtained by exhaustive reduction of keto alcohol **8a** with $LiEt_3BH$ (91%)[14] followed by hydrogenolysis of the resulting triol **10** (quantitative). In this way, **1**·HCl, which showed spectral properties identical to those reported in the literature,[4a] was prepared in six steps from hydroxyproline **6** with a 61% overall yield.

The synthesis of the rest of the desired glycosidase inhibitors, **2**−**5**, called for a more demanding strategy since it required both flexibility (to introduce the different carbon appendages) and stereocontrol (to produce the correct configurations at the C2″ chiral centers). We thought that the sequence of transformations: ester **9** to ketone (**11**) to alcohol (**13** or **14**) could offer the opportunity to fulfill both objectives. The attractiveness of this synthetic scheme was further increased by our serendipitous discovery that the reaction of organolithium reagents with certain *N*-(9-phenylfluoren-9-yl)-amino esters afforded the corresponding enantiomerically pure amino ketones in high yields.[15] We thus decided to explore the reaction of *N*-Pf proline ester **9c**, prepared from **9a** in 97% yield (2,2-dimethoxypropane, cat. PPTS), with organolithium reagents.

The reaction of **9c** with MeLi was used to optimize the experimental conditions to provide the ketones **11a**−**c**. Surprisingly, when **9c** was treated with 120 mol % of MeLi (THF, −78 °C, 90 min) no reaction occurred; only when the amount of MeLi was raised over 200 mol % (220 mol %, −78 °C, 105 min) was ketone **11a** formed in good yield (88%), along with tertiary alcohol **12** (10%).

(11) Molecular mechanics and semiempirical calculations on various *N*-Pf-$\Delta^{3,4}$ dehydroproline model systems showed that the CO_2Me group is locked in an axial position and that one of the *ortho* hydrogens of the phenyl ring of the Pf group effectively blocks the *Re* face of the $\Delta^{3,4}$ double bond.

(12) Blanco, M. J.; Sardina, F. J. *Tetrahedron Lett.* **1994**, *35*, 8493.

(13) The rest of the material isolated from this reaction was mostly unreacted ketone **7**.

(14) The use of DIBAL, Red-Al, or $LiAlH_4$ led to the formation of small amounts of the C4 epimer of **10**.

(15) Fernández-Megía, E.; Iglesias-Pintos, J. M.; Sardina, F. J. Unpublished results.

We attributed the lack of reactivity of equimolar amounts of MeLi toward the carboxymethyl group of **9a** to a complexation of the organometallic reagent with the dioxolane group of **9c**. In order to break this complexation we used HMPA (300 mol %), and indeed, some alkylation was seen even with 100 mol % of MeLi: **11a** was obtained in 25% yield, along with 60% of recovered **9a** and traces of **12**. The best results were, however, obtained when $LiClO_4$ (500 mol %) was used to saturate all possible coordination sites of **9a** (and perhaps to activate the carboxy group): 125 mol % of MeLi afforded (−78 °C, 2 h) 90−97% yields of ketone **11a** unaccompanied by alcohol **12**. When these optimized conditions were applied to the reaction of **9c** with $LiCH_2OMOM$[16] the desired ketone **11b** was obtained in 79% yield; no trace of the corresponding tertiary alcohol was detected.

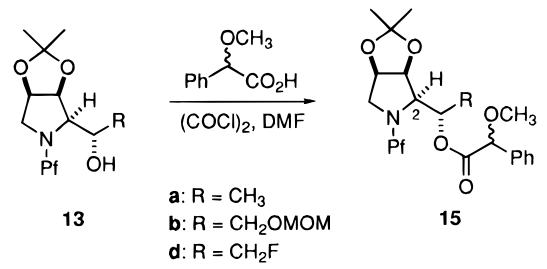
To introduce the side chain required for the synthesis of indolizidines **5a**,**b** we deemed that a Grignard reagent would be a far easier nucleophile to prepare than the corresponding organolithium species; thus, we decided to study the feasibility of preparing the ketones **11** by the reaction of **9c** with organomagnesium nucleophiles. When **9c** was treated with MeMgBr (300 mol %, −40 °C) methyl ketone **11a** was isolated in 75% yield, accompanied by 25% of recovered **9c**. In this case the addition of $LiClO_4$ did not affect the outcome of the reaction. When $(CH_2O)_2CHCH_2CH_2MgBr$[17] was substituted for MeMgBr (300 mol %, −40 to −5 °C) as the nucleophile, ketone **11c** was isolated in 96% yield; no trace of the corresponding tertiary alcohol was detected.

We believe that the success of these transformations results from the interplay of several factors: the electron-poor nature of the carboxyl group of **9c** (α,β,γ-trisubstituted by electron-withdrawing groups) and the presence of Li^+ complexing substituents at C3 and N.[18] In this respect it is worthy of note that *N*-Pf-proline gives mainly the corresponding tertiary alcohol when treated with MeLi (150 mol %, 500 mol % of $LiClO_4$, 2 h).

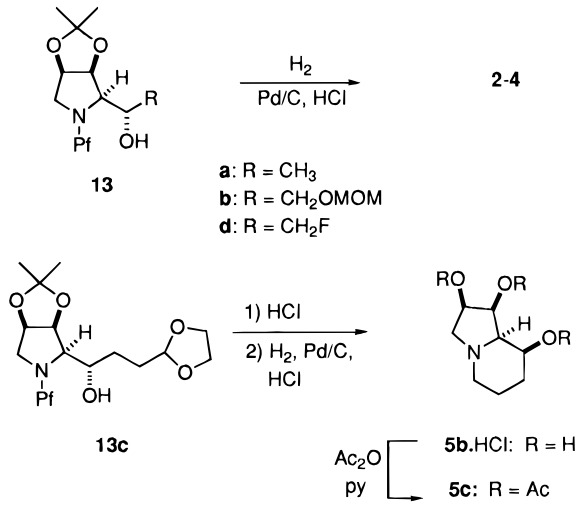
Fluoro ketone **11d** was prepared in 65% yield (87% based on recovered starting material) by fluorination of the kinetic enolate of methyl ketone **11a** (NaHMDS, 150 mol %, THF, −78 °C) with $(PhSO_2)_2NF$ (160 mol %).[19]

The last synthetic hurdle in our approach to the glycosidase inhibitors **2**−**5** was the stereoselective reduction of ketones **11** to the alcohols (**13** or **14**) with the appropriate configuration at the side chain. The results of the reactions of ketones **11a**−**d** with several hydrides are shown in Scheme 2. Methyl ketone **11a** could be stereoselectively reduced to provide alcohols **13a** or **14a** with complete stereocontrol. The rest of the ketones could be reduced stereoselectively, but the degree of stereocontrol was not absolute. The configurations of the newly created stereogenic centers in **13a**,**b**,**d** were determined by application of the empirical method for the establishment of the absolute configuration of secondary alcohols developed by Trost and co-workers.[20] Thus, **13a**,**b**,**d** were esterified with both (*R*)- and (*S*)-*O*-methylmandelic acids ($(COCl)_2$, DMF) to give esters **15a**,**b**,**d**

Scheme 3



Scheme 4



in good to excellent yields. Analysis of the chemical shifts of H-2 and the hydrogens on the side chains of *O*-mandelates **15** allowed us to assign the configuration shown in Scheme 3 to alcohols **13a**,**b**,**d**. The configuration of alcohol **13c** was established by correlation with 8-*epi*-swainsonine **5b**, as discussed below.

Hydrogenolysis in an acidic media (Pd/C (10%), MeOH−HCl) of **13a**,**b**,**d** and **14a**,**b**,**d** was all that was needed to obtain the desired glycosidase inhibitors **2**−**4** (as the corresponding hydrochlorides) in quantitative yields. Pyrrolidine **3a**·HCl exhibited spectral properties identical to those reported in the literature,[21] as did compounds **2a**·HCl[22] and **2b**·HCl.[4a]

The indolizidine glycosidase inhibitor 8-*epi*-swainsonine (**5b**) was obtained in 94% yield by treatment of **13c** with aqueous HCl (5%) followed by hydrogenolysis (Pd/C (10%), MeOH, HCl), with concomitant reductive cyclization of the resulting crude *N*-Pf-amino aldehyde (Scheme 4). The triacetate of **5b** showed spectral and physical properties identical to those reported in the literature.[23]

Conclusions

We have developed a short, efficient, and stereoselective synthesis of polyhydroxylated pyrrolidine and indolizidine glycosidase inhibitors starting from 4-hydroxy-L-proline. The regio- and stereoselective hydroxylation of a *N*-Pf-4-oxoproline enolate and the stereoselective reduction of the resulting keto alcohol allowed us to introduce the *cis* diol present in the target compounds.

(16) Generated *in situ* from the reaction of Bu_3SnCH_2OMOM with nBuLi: Johnson, C. R.; Medich, J. R. *J. Org. Chem.* **1988**, *53*, 4131.
(17) Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122.
(18) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934.
(19) Differding, E.; Ofner, H. *Synlett* **1991**, 187.
(20) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
(21) Stevens, C. L.; Glinski, R. P.; Taylor, K. G.; Blumbergs, P.; Gupta, S. K. *J. Am. Chem. Soc.* **1970**, *92*, 3160.
(22) Bashyal, B. P.; Fleet, G. W. J.; Gough, M. J.; Smith, P. W. *Tetrahedron* **1987**, *43*, 3083.
(23) Tadano, K.-I.; Iimura, Y.; Hotta, Y.; Fukabori, C.; Suami, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3885.

The different side chains needed to complete the syntheses of the target compounds were introduced by reduction of the ester group of a susbtituted proline or by reaction of organolithium or organomagnesium reagents with the same group followed by stereoselective reduction of the resulting ketones. Hydrogenolysis of the alcohols thus obtained gave the hydrochlorides of the desired pyrrolidine glycosidase inhibitors, which were obtained in nine steps in overall yields greater than 50%. The indolizidine glycosidase inhibitor 8-*epi*-swainsonine was also prepared using this approach.

Experimental Section

General Methods. All the reactions were carried out under an atmosphere of dry argon, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone inmediately before use; methylene chloride, triethylamine, CH_3CN, pyridine, DMF, and trimethylsilyl chloride were distilled from CaH_2; methanol was distilled from magnesium and acetone from $CaCO_3$. Column chromatography was performed with 230−400 (low-pressure chromatography) and 70−230 (gravity chromatography) mesh silica gel. Thin-layer chromatography (TLC) was done on silica 60/F-254 aluminium-backed plates (E. Merck). Melting points are uncorrected.

(2*S*,4*R*)-4-Hydroxypyrrolidine-2-carboxylic Acid Methyl Ester Hydrochloride (6a). Thionyl chloride (7.8 mL, 106.8 mmol, 140 mol %) was added dropwise to a suspension of *trans*-4-hydroxy-L-proline (**6**) (10.0 g, 76.3 mmol) in MeOH (52 mL) at 0 °C. The bath was removed, and the solution was allowed to stir at room temperature for 74 h and then concentrated. The residual oil was triturated with ether, and the resulting white crystalline solid was filtered, washed with cold ether, and dried to give 13.9 g (100%) of **6a**, which was recrystallized from MeOH/EtOAc to give **6a** as colorless needles: ^{1}H NMR (MeOD-d_4) δ 2.20 (m, 1H), 2.42 (m, 1H), 3.31 (m, 1H), 3.44 (d, J = 11, 8 Hz, 1H), 3.86 (s, 3H), 4.61 (m, 2H); ^{13}C NMR (MeOD-d_4) δ 38.6, 54.0, 55.0, 59.5, 70.6, 170.7.

(2*S*,4*R*)-4-Hydroxy-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (6b). A mixture of **6a** (2.20 g, 12.1 mmol) and chlorotrimethylsilane (3.8 mL, 30.3 mmol, 250 mol %) in CH_2Cl_2 (30 mL) in a Morton flask at 0 °C was treated with triethylamine (5.9 mL, 42.4 mmol, 350 mol %) and allowed to reach room temperature. The mixture was stirred while refluxing for 1 h, cooled to 0 °C, treated with MeOH (0.74 mL, 18.2 mmol, 150 mol %) in CH_2Cl_2 (3,3 mL), allowed to warm to room temperature for 1 h, and then treated with PfBr (5.05 g, 15.7 mmol, 130 mol %), triethylamine (1.7 mL, 12.1 mmol, 100 mol %), and $Pb(NO_3)_2$ (3.6 g, 10.9 mmol, 90 mol %). The mixture was stirred at room temperature for 96 h, filtered, and evaporated. The remaining solid was redissolved in MeOH (40 mL) and citric acid (4 g) was added; the mixture was vigorously stirred for 1 h. Solvent was evaporated, and the remaining solid was chromatographed with EtOAc/hexane 1/1 as eluant to provide 3.84 g (82%) of **6b** as a white foam: $[\alpha]^{25}_D$ = +143.2 (*c* 1.37, Cl_3CH); IR (CH_3Cl) 3619, 3019, 1735; ^{1}H NMR (Cl_3CD) δ 1.81 (m, 1H), 1.98 (m, 1H), 2.93 (dd, J = 5.3, 10.6 Hz, 1H), 3.24 (s, 3H), 3.30 (dd, J = 5.8, 9.0 Hz, 1H), 3.60 (dd, J = 5.2, 10.0 Hz, 1H), 4.51 (q, J = 5.4 Hz, 1H), 7.12−7.76 (m, 13 H); ^{13}C NMR (Cl_3CD) δ 39.9, 51.3, 56.8, 59.3, 70.3, 119.8, 120.1, 126.4, 127.1, 127.2, 127.3, 127.6, 128.3, 128.4, 128.7, 139.9, 141.5, 142.7, 146.1, 147.2, 175.9. Anal. Calcd for $C_{25}H_{23}O_3N$: C, 77.9; H, 6.0; N, 3.6. Found: C, 77.6; H, 6.2; N, 3.4.

(2*S*)-4-Oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (7). DMSO (5.0 mL, 71.09 mmol, 520 mol %) was added to a solution of oxalyl chloride (3.1 mL, 35.76 mmol, 260 mol %) in CH_2Cl_2 (60 mL) at −60 °C. After being stirred for 5 min, a solution of **6b** (5.3 g, 13.75 mmol) in CH_2Cl_2 (90 mL) was added. The mixture was stirred for 30 min at −60 °C, treated with 44 mL of triethylamine, and allowed to reach room temperature. $NaHCO_3$ (saturated) (200 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL), and the combined organic layers were washed with brine (350 mL), dried, filtered, and evaporated to an oil, which was chromatographed (silica 70−230 mesh) with EtOAc/hexane 1:4 as eluant to give 5.26 g (100%) of **7**. Recrystallization from Et_2O/hexane provided **7** as a white solid: mp 136−138 °C; $[\alpha]^{25}_D$ = −64.2° (*c* 1.42, Cl_3CH); IR (NaCl) 3057, 1756, 1728, 1266; ^{1}H NMR (Cl_3CD) δ 2.28 (dd, J = 2.8, 19.0 Hz, 1H), 2.45 (dd, J = 9.0, 17.9 Hz, 1H), 3.20 (s, 3H), 3.48 (d, J = 17.9 Hz, 1H), 3.76 (dd, J = 3.1, 8.6 Hz, 1H), 3.77 (d, J = 17.8 Hz, 1H), 7.23−7.48 (m, 11H), 7.71 (m, 2H); ^{13}C NMR (Cl_3CD) δ 41.6, 51.5, 55.2, 58.2, 76.0, 120.1, 120.3, 125.5, 126.9, 127.0, 127.6, 127.7, 128.0, 128.6, 128.8, 128.9, 140.3, 140.9, 141.8, 145.3, 146.5, 173.1, 212.9. Anal. Calcd for $C_{25}H_{21}O_3N$: C, 78.3; H, 5.5; N, 3.6. Found: C, 78.0; H, 5.6; N, 3.6.

(2*S*,3*S*)-3-Hydroxy-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (8a). A solution of **7** (1.47g, 3.82 mmol) in THF (37 mL) was added dropwise (in 25 min) to a stirred solution of NaHMDS (5.7 mL, 5.7 mmol, 150 mol %, 1.0 M in THF) in THF (13 mL) at −78 °C; the resulting solution was stirred for 1.5 h at −78 °C, and then MoOPH (1.77 g, 4.08 mmol, 175 mol %) was added and the stirring was continued for 2.5 h from −78 to −15 °C. The reaction was quenched at −15 °C with saturated Na_2SO_3 (2 mL). The resulting suspension was allowed to reach room temperature. The suspension was partitioned between H_2O (30 mL) and Et_2O (40 mL); the organic phase was washed with HCl (30 mL, 5% aqueous) and brine (40 mL); the aqueous phase was reextracted with Et_2O (2 × 40 mL), and the combined organic layers were dried and concentrated to give a residue that was purified by column chromatography (hexane/EtOAc, 2/1) to give 1.26 g (82%) of **8a** and 55 mg (4%) of **7**. The compound **8a** was recrystallized as a colorless solid from EtOAc/hexane: mp 180−182 °C; $[\alpha]^{25}_D$ = −199.8 (*c* 1.04, Cl_3CH); IR (NaCl) 3592, 1769, 1741; ^{1}H NMR (Cl_3CD) δ 3.13 (s, 3H), 3.65 (d, J = 17.7 Hz, 1H), 3.88 (d, J = 17.8 Hz, 1H), 3.95 (d, J = 7.9 Hz, 1H), 4.41 (d, J = 7.9 Hz, 1H), 7.21−7.44 (m, 11 H), 7.66−7.75 (m, 2H); ^{13}C NMR (Cl_3CD) δ 51.3, 51.8, 61.9, 74.9, 75.1, 120.2, 120.3, 125.2, 126.6, 126.8, 127.7, 127.9, 128.1, 128.7, 129.0, 139.9, 141.1, 141.3, 145.2, 146.7, 171.0, 211.8. Anal. Calcd for $C_{25}H_{21}O_4N$: C, 75.2; H, 5.3; N, 3.5. Found: C, 75.2; H, 5.4; N, 3.5.

(2*S*,3*S*,4″*R*)- and (2*S*,3*S*,4″*S*)-3-[(Phenylethyl)carbamoyl]-4-oxo-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester. (**8b**, **8c**). (*R*)-Ph(CH_3)CHNCO (36 μL, 0.255 mmol, 200 mol %) was added to a suspension of **8a** (51 mg, 0.128 mmol) and CuBr·SMe_2 (79 mg, 0.384 mmol, 300 mol %) in THF (3 mL). Stirring was continued for 5 h at rt, and then AcOEt (2 mL) was added. The reaction mixture was washed with a solution of NH_4Cl/NH_3 pH = 8 (2 × 10 mL). The aqueous layer was extracted with AcOEt (2 × 15 mL). The combined organic layers were washed consecutively with H_2O (15 mL) and brine (25 mL), dried, and concentrated. The residue was purified by column chromatography (EtOAc/hexane 1/3) to afford 70 mg (100%) of **8c** as a white foam. **8c**: $[\alpha]^{25}_D$ = −116° (*c* 1.39, Cl_3CH); IR (NaCl) 3343, 1775, 1734; ^{1}H NMR (Cl_3CD) δ 1.38 (d, J = 6.9 Hz, 3H), 3.19 (s, 3H), 3.52 (d, J = 17.7 Hz, 1H), 3.86 (d, J = 17.7 Hz, 1H), 4.15 (d, J = 8.0 Hz, 1H), 4.73 (m, 1H), 5.10 (d, J = 7.4 Hz, 1H), 5.41 (d, J = 8.0 Hz, 1H), 7.25−7.75 (m, 18 H); ^{13}C NMR (Cl_3CD) δ 22.1, 51.0, 51.4, 52.0, 60.5, 74.2, 75.2, 120.2, 120.3, 125.3, 125.9, 126.5, 126.7, 127.5, 127.7, 127.9, 128.3, 128.6, 128.7, 129.0, 139.5, 141.0, 141.4, 142.5, 144.8, 146.5, 153.7, 170.4, 206.7. Anal. Calcd for $C_{34}H_{30}O_5N_2$: C, 74.7; H, 5.5; N, 5.1. Found: C, 74.9; H, 5.6; N, 5.1. In an analogous way, **8b** was prepared using (*S*)-Ph(CH_3)CHNCO. **8b**: $[\alpha]^{25}_D$ = −136.5° (*c* 1.07, Cl_3CH), IR (NaCl) 3396, 1773, 1723; ^{1}H NMR (Cl_3CD) δ 1.41 (d, J = 6.8 Hz, 3H), 3.10 (s, 3H), 3.52 (d, J = 17.5 Hz, 1H), 3.86 (d, J = 17.8 Hz, 1H), 4.10 (d, J = 8.1 Hz, 1H), 4.75 (m, 1H), 5.14 (d, J = 7.5 Hz, 1H), 5.43 (d, J = 8.0 Hz, 1H), 7.16−7.74 (m, 18 H); ^{13}C NMR (Cl_3CD) δ 22.1, 50.9, 51.3, 52.1, 60.4, 74.1, 75.3, 120.2, 120.3, 125.4, 125.8, 126.6, 126.8, 127.5, 127.7, 127.9, 128.4, 128.7, 128.8, 129.1, 139.6, 141.2, 141.4, 142.9, 145.0, 146.6,; 153.7, 170.5, 207.1. Anal. Calcd for $C_{34}H_{30}O_5N_2$: C, 74.7; H, 5.5; N, 5.1. Found: C, 74.4; H, 5.6; N, 5.1.

(2*R*,3*S*,4*R*)-3,4-Dihydroxy-2-(hydroxymethyl)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (10). $LiEt_3BH$ (1.3 mL, 1.19 mmol, 500 mol %, 0.89 M in THF) was added to a solution of **8a** (95 mg, 0.238 mmol) in THF (1.9 mL) at −78 °C. The reaction mixture was stirred 45 min at −78 °C and 2 h at rt. The reaction was worked up with a solution of H_2O_2 (30%, 1.5 mL) in aqueous LiOH (5%) at 0 °C in order to break up the intermediate boronate ester. After that, the bath was removed and the stirring was continued for 2 h at rt. The reaction mixture was cooled to 0 °C again, and Na_2SO_3 (saturated) (1 mL) was added and stirred for 15 min. The resulting suspension was partitioned between Na_2SO_3 (saturated) (30 mL) and CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine (40 mL), dried, and concentrated. The residue was purified by column chromatography (70−230 mesh silica gel, AcOEt/hexane 1/1.6) to give 81 mg (91%) of **10**. Recrystallization from AcOEt/hexane resulted in colorless needles: mp 174 °C dec; $[\alpha]^{25}_D = +313.6$ (*c* 1.06, Cl_3CH); IR (NaCl) 3287, 1451, 1121; ^{1}H NMR (Cl_3CD) δ 2.60 (dd, J = 4.3, 11.0 Hz, 1H), 2.69 (dd, J = 4.2, 8.0 Hz, 1H), 3.21 (dd, J = 5.1, 11.9 Hz), 3.32 (dd, J = 2.7, 11.9 Hz, 1H), 3.36 (d, J = 11.1 Hz, 1H), 3.87 (dd, J = 4.9, 8.0 Hz, 1H), 3.97 (m, 1H), 7.19−7.75 (m, 13H); ^{13}C NMR (Cl_3CD) δ 55.4, 59.8, 59.9, 70.9, 73.4, 76.6, 120.1, 120.2, 125.5, 125.9, 127.4, 127.5, 127.9, 128.0, 128.5, 128.6, 128.9, 139.1, 141.8, 142.2, 146.5, 148.9. Anal. Calcd for $C_{24}H_{23}O_3N$: C, 77.2; H, 6.2; N, 3.7. Found: C, 76.9; H, 6.5; N, 3 .6.

(2*R*,3*S*,4*R*)-3,4-Dihydroxy-2-(hydroxymethyl)pyrrolidine Hydrochloride (1·HCl). Pd/C (17 mg, 30 wt %, 10%) and HCl (concd) (0.1 mL) were added to a solution of **10** (58 mg, 0.16 mmol) in deoxygenated MeOH (2 mL). The flask was purged with argon and then evacuated (vacuum) and pressurized (H_2) three times. The reaction mixture was mechanically shaken under 52 psi of H_2 for 10 h. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was washed with toluene to give a clear yellow oil that was recrystallized from methanol/AcOEt to afford 26 mg of **1·HCl** (100%) as a white solid: mp 157−159 °C; $[\alpha]^{20}_D$ = +19.0° (*c* 0.60, H_2O); IR (KBr) 3392, 2940, 1550, 1450; ^{1}H NMR (D_2O) δ 3.07 (dd, J = 12.1, 7.3 Hz, 1H), 3.40 (dd, J = 7.3, 12.1 Hz, 1H), 3.62 (m, 1H), 3.75 (dd, J = 8.2, 12.1 Hz, 1H), 3.86 (dd, J = 5.1, 12.1 Hz, 1H), 4.21 (t, J = 4.1 Hz, 1H), 4.36 (dt, J = 4.1, 7.3 Hz, 1H); ^{13}C NMR (D_2O, ref dioxane) δ 10.0, 13.3, 12.1, 13.1, 12.5. Anal. Calcd for $C_5H_{11}O_3NCl$: C, 35.6; H, 6.6; N, 8.3. Found: C, 35.3; H, 6.8; N, 8.0.

(2*S*,3*S*,4*R*)-3,4-Dihydroxy-*N*-(9′-phenylfluoren-9′-yl)-pyrrolidine-2-carboxylic Acid Methyl Ester (9a). $NaBH_4$ (13 mg, 0.426 mmol, 200 mol %) was added to a solution of **8a** (85 mg, 0.213 mmol) in MeOH/THF (1/1, 2.2 mL) at −78 °C; the resulting suspension was stirred for 4 h at −78 °C, and then the reaction was quenched with a few drops of H_3PO_4 (10%) and allowed to reach room temperature. The suspension was partitioned between H_2O (10 mL) and Cl_3CH (10 mL). The aqueous phase was extracted with Cl_3CH (2 × 10 mL), and the combined organic layers were washed with brine (20 mL), dried, and concentrated to give a residue that was purified by column chromatography (hexanes/EtOAc 1/1) to give 79 mg (92%) of **9a** as a white foam: $[\alpha]^{25}_D = +223.3°$ (*c* 1.39, Cl_3CH); IR (CH_3Cl), 3021, 1722, 1217; ^{1}H NMR(Cl_3CD) δ 2.83 (br d, J = 8.8 Hz, 1H), 2.97 (dd, J = 2.8, 10.4 Hz, 1H), 3.18 (d, J = 9.0 Hz, 1H), 3.31 (s, 3H), 3.41 (d, J = 10.4 Hz, 1H), 3.94 (m, 2H), 4.11 (d, J = 11.8 Hz, 1H), 7.12−7.77 (m, 13H); ^{13}C NMR (Cl_3CD) δ 51.9, 53.0, 62.6, 71.9, 72.7, 75.4, 120.0, 120.3, 126.4, 126.8, 127.2, 127.3, 127.5, 127.6, 128.4, 128.5, 128.9, 139.3, 140.9, 141.8, 144.5, 147.5, 175.8. Anal. Calcd for $C_{25}H_{23}O_4N$: C, 74.8; H, 5.8; N, 3.5. Found: C, 74.5; H, 5.8; N, 3.4.

(2*S*,3*S*,4*R*)-3,4-Diacetoxy-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (9b). To a suspension of **9a** (45 mg, 0.112 mmol) and DMAP (cat.) in Ac_2O (0.5 mL) was added pyridine (0.5 mL), and the mixture was stirred at rt for 3 h. A few drops of $NaHCO_3$ (saturated) were added to the reaction mixture, which was partitioned between $NaHCO_3$ (saturated) (10 mL) and AcOEt/hexane (15 mL). The aqueous layer was reextracted with AcOEt/hexane (2 × 15 mL), and the combined organic layers were washed with brine (30 mL), dried, and concentrated. The residue was purified by chromatography on silica gel (AcOEt/hexane 1/4) to afford 28 mg (52%) of **9b** as a white foam: $[\alpha]^{25}_D = +174.9$ (*c* 1.33, Cl_3CH); IR (NaCl) 2958, 1748, 1750, 1449; ^{1}H NMR (Cl_3CD) δ 2.00 (s, 3H), 2.03 (s, 3H), 3.36 (s, 3H), 3.40 (d, J = 6.9 Hz, 1H), 3.45 (d, J = 6.6 Hz, 2H), 5.00 (td, J = 4.8, 6.6 Hz, 1H), 5.22 (dd, J = 4.8, 6.9 Hz, 1H), 7.12−7.75 (m, 13H); ^{13}C NMR (Cl_3CD) δ 20.6, 20.7, 51.3, 51.4, 51.5, 62.0, 71.0, 72.3, 119.8, 120.2, 125.7, 127.2, 127.3, 127.5, 128.4, 128.5, 128.6, 129.1, 139.5, 141.7, 142.7, 145.7, 146.8, 169.7, 170.3, 171.1. Anal. Calcd for $C_{29}H_{27}O_6N$: C, 71.7; H, 5.6; N, 2.9. Found: C, 71.6; H, 5.8; N, 2.8.

(2*S*,3*S*,4*R*)-3,4-(Isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine-2-carboxylic Acid Methyl Ester (9c). A solution of **9a** [(310 mg, 0.772 mmol) in DMF (2.1 mL) and acetone (0.7 mL)] and 2,2-dimethoxypropane (0.242 mL, 1.93 mmol, 250 mol %) was stirred with PPTS (14 mg, 0.05 mmol, 7 mol %) at 5 °C for 24 h. The mixture was partitioned between brine (5 mL) and CH_2Cl_2 (3 × 5 mL). The combined organic layer was concentrated, the oily residue was redissolved in Et_2O (10 mL), and the organic layer was washed with H_2O (2 × 5 mL). The combined organic layers were dried, filtered, and evaporated. The residue was purified by chromatography (EtOAc/hexane 1/5) to afford 330 mg (97%) of **9c** as a white foam: $[\alpha]^{25}_D = 32.9°$ (*c* 1.21, Cl_3CH); IR (NaCl) 2953, 1767, 1453; ^{1}H NMR (Cl_3CD) δ 1.24 (s, 3H), 1.47 (s, 3H), 3.21 (dd, J = 5.5, 11.5 Hz, 1H), 3.32 (s, 3H), 3.38 (d, J = 7.2 Hz, 1H), 3.54 (dd, J = 2.9, 11.5 Hz, 1H), 4.61 (m, 2H), 7.15−7.72 (m, 13H); ^{13}C NMR (Cl_3CD) δ 25.2, 26.0, 50.8, 53.5, 65.5, 76.1, 79.3, 80.6, 113.5, 119.6, 120.1, 126.2, 127.1, 127.2, 127.3, 127.5, 127.6, 128.4, 128.7, 139.7, 141.3, 142.3, 146.0, 147.2, 171.1. Anal. Calcd for $C_{28}H_{27}O_4N$: C, 76.2; H, 6.2; N, 3.2. Found: C, 75.9; H, 6.2; N, 3.0.

(2*S*,3*S*,4*R*)-2-(1″-Oxoethyl)-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (11a). MeLi (0.38 mL, 0.62 mmol, 1.6 M in ether, 150 mol %) was added dropwise to a stirred solution of **9c** (182 mg, 0.41 mmol) and $LiClO_4$ (219 mg, 2.06 mmol, 500 mol %) in THF (5.5 mL) at −78 °C. The resulting yellow solution was stirred for 2.5 h, and then a few drops of H_3PO_4 (10%) were added. The suspension was partitioned between H_2O (7 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried and concentrated to give a residue that was purified by column chromatography (hexane/EtOAc 5/1) to give 155 mg (89%) of **11a** as a white foam: $[\alpha]^{22}_D = 206.4°$ (*c* 1.22, Cl_3CH); IR (NaCl) 2955, 1734, 1712; ^{1}H NMR (Cl_3CD) δ 1.20 (s, 3H), 1.48 (s, 3H), 1.97 (s, 3H), 3.21 (d, J = 6.9 Hz, 1H), 3.36 (dd, J = 6.7, 12.6 Hz, 1H), 3.51 (dd, J = 3.8, 12.9 Hz, 1H), 4.55 (m, 2H), 7.11−7.74 (m, 13H); ^{13}C NMR (Cl_3CD) δ 24.9, 26.4, 28.6, 55.4, 71.1, 77.1, 79.8, 81.5, 113.1, 119.9, 120.2, 125.9, 126.9, 127.4, 127.5, 127.6, 127.9, 128.5, 128.7, 128.9, 139.5, 141.7, 142.7, 146.5, 148.2, 208.2. Anal. Calcd for $C_{28}H_{27}O_3N$: C, 79.0; H, 6.4; N, 3.3. Found: C, 78.8; H, 6.4; N, 3.0. Compound **12** was isolated in order to be identified. Flash chromatography (hexanes/AcOEt 7/1) afforded **12** as a white foam. **12**: $[\alpha]^{25}_D = 312.6°$ (*c* 1.4, Cl_3CH); IR (NaCl) 3579, 2935, 1449; ^{1}H NMR (Cl_3CD) δ 0.94 (s, 3H), 1.15 (s, 3H), 1.30 (s, 3H), 1.48 (s, 3H), 2.63 (d, J = 7.9 Hz, 1H), 3.43 (dd, J = 6.2, 14.3 Hz, 1H), 3.62 (m, 2H), 3.82 (t, J = 8.0 Hz, 1H), 4.79 (dd, J = 14.2, 7.7 Hz, 1H), 7.06−7.73 (m, 13H); ^{13}C NMR (Cl_3CD) δ 23.4, 25.5, 27.3, 30.2, 55.6, 67.4, 74.0, 78.5, 81.9, 83.4, 114.3, 119.5, 120.4, 125.5, 127.3, 127.3, 127.5, 127.6, 128.3, 128.5, 129.2, 139.8, 141.8, 143.5, 148.5, 148.6. Anal. Calcd for $C_{29}H_{31}O_3N$: C, 78.9; H, 7.1; N, 3.2. Found: C, 78.5; H, 7.2; N, 2.9.

(2*S*,3*S*,4*R*)-2-[2″-(Methoxymethoxy)-1″-oxoethyl]-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (11b). *n*-BuLi (0.410 mL, 0.567 mmol, 1.4 M in hexane, 250 mol %) was added to a stirred solution of Bu_3SnCH_2OMOM (207 mg, 0.567 mmol, 250 mol %) in THF (3.5 mL) at −78 °C over a period of 2 min while the temperature was maintained below −65 °C. Stirring was continued for no more than 5 min,[16] at which time a solution of **9c** (100 mg, 0.227 mmol) and $LiClO_4$ (121 mg, 1.14 mmol, 500 mol %) in THF (4 mL) was added dropwise. The resulting yellow solution was stirred for 2 h at −78 °C, and then the reaction was quenched by the addition of saturated NH_4Cl solution (0.25 mL). The suspen-

sion was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried and evaporated. The crude product was purified by chromatography (hexane/EtOAc 4/1) to give 87 mg (79%) of **11b**: $[\alpha]^{22}_D = 120.2°$ (*c* 1.31, Cl_3CH); IR (NaCl) 2942, 1737, 1449; ^1H NMR (Cl_3CD) δ 1.19 (s, 3H), 1.43 (s, 3H), 3.29 (s, 3H), 3.47 (m, 3H), 3.82 (d, J = 17.3 Hz, 1H), 4.17 (d, J = 17.3 Hz, 1H), 4.48 (dd, J = 6.6, 9.0 Hz, 2H), 4.56 (d, J = 4.4 Hz, 2H), 7.12−7.73 (m, 13H); ^{13}C NMR (Cl_3CD) δ 25.1, 26.3, 55.2, 55.4, 67.8, 71.5, 77.1, 80.2, 81.4, 96.1, 113.6, 119.8, 120.1, 125.8, 126.9, 127.4, 127.5, 127.9, 128.0, 128.5, 128.6, 128.9, 139.4, 141.6, 142.7, 146.8, 148.3, 205.9. Anal. Calcd for $C_{30}H_{31}O_5N$: C, 74.2; H, 6.5; N, 2.9. Found: C, 74.0; H, 6.7; N, 2.7.

(2*R*,3*S*,4*R*,1″*R*)-2-(1″-Hydroxyethyl)-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (14a). K-Selectride (0.71 mL, 0.7 mmol, 1.0 M in THF, 150 mol %) was added to a stirred solution of **11a** (200 mg, 0.47 mmol) in THF (4 mL). The stirring was continued for 14h at room temperature. The reaction mixture was partitioned between H_2O (20 mL) and CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were dried and evaporated. The crude product was purified by chromatography (70−230 mesh silica gel, hexane/EtOAc 5/1) to give 200 mg (100%) of **14a** as a white foam: $[\alpha]^{25}_D$ = 214.0° (*c* 0.63, Cl_3CH); IR (NaCl) 3523, 2931, 1450; ^1H NMR (Cl_3CD) δ 1.18 (d, J = 6.5 Hz, 3H), 1.22 (s, 3H), 1.55 (s, 3H), 2.36 (t, J = 6.6 Hz, 1H), 3.19 (d, J = 5.2 Hz, 2H), 3.65 (br s, 1H), 3.73 (m, 1H), 4.02 (t, J = 6.6 Hz, 1H), 4.62 (m, 1H), 7.15−7.73 (m, 13H); ^{13}C NMR (Cl_3CD) δ 20.9, 24.5, 25.9, 55.0, 66.2, 66.6, 77.1, 80.2, 83.1, 113.5, 119.7, 120.3, 125.4, 127.3 (3C), 127.4, 127.5, 127.8, 128.3 (2C), 128.5, 128.8, 139.8, 141.1, 143.4, 147.5, 148.9. Anal. Calcd for $C_{28}H_{29}O_3N.1.5\ H_2O$: C, 74.0; H, 7.1; N, 3.1. Found: C, 74.1; H, 6.7; N, 2.7.

(2*R*,3*S*,4*R*,1″*S*)-2-(1″-Hydroxyethyl)-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (13a). $LiEt_3BH$ (1.47 mL, 1.30 mmol, 1.0 M in THF, 150 mol %) was added dropwise to a stirred solution of **11a** (370 mg, 0.87 mmol) in THF (7 mL) at 0 °C. The stirring was continued at 0 °C for 3 h, and then AcOEt (0.25 mL) was added. The reaction mixture was partitioned between H_2O (35 mL) and CH_2Cl_2 (35 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL), and the combined organic layers were dried and evaporated. The crude product was purified by chromatography (70−230 mesh silica gel, hexane/EtOAc 5/1) to give 370 mg (100%) of **13a** as a white foam: $[\alpha]^{25}_D = 254.2°$ (*c* 0.51, Cl_3CH); IR (NaCl) 3557, 2932, 1448; ^1H NMR (Cl_3CD) δ 0.98 (d, J = 5.9 Hz, 3H), 1.15 (s, 3H), 1.42 (s, 3H), 2.36 (t, J = 7.6 Hz, 1H), 3.25 (m, 1H), 3.48 (dd, J = 6.9, 13.9 Hz, 1H), 3.73 (m, 2H), 4.67 (c, J = 7.0 Hz, 1H), 7.19−7.75 (m, 13H); ^{13}C NMR (Cl_3CD) δ 20.6, 24.4, 25.5, 54.1, 64.2, 66.7, 77.3, 81.2, 81.9, 113.9, 119.7, 120.4, 125.1, 126.6, 127.0, 127.3, 127.6, 128.0, 128.2, 128.5, 128.7, 129.2, 139.5, 141.3, 143.1, 148.0, 148.8. Anal. Calcd for $C_{28}H_{29}O_3N{\cdot}0.5H_2O$: C, 77.0; H, 6.9; N, 3.2. Found: C, 77.0; H, 7.3; N, 2.8.

(2*R*,3*S*,4*R*,1″*S*)-2-(Hydroxyethyl)-3,4-dihydroxypyrrolidine Hydrochloride (3b·HCl). Pd/C (37 mg, 30 wt %, 10%) and concd HCl (0.2 mL) were added to a solution of **13a** (122 mg, 0.285 mmol) in deoxygenated MeOH (4 mL). The flask was purged with argon and then evacuated (vacuum) and pressurized (H_2) three times. The reaction mixture was mechanically shaken under 52 psi of H_2 for 10 h. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was washed with toluene to give a yellow oil which was recrystallized from ethanol/ether to afford 52 mg of **3b·HCl** (100%) as a white solid: mp 185−187 °C; $[\alpha]^{25}_D = 15.1°$ (*c* 0.40, MeOH); IR (KBr) 3600, 3110, 2940, 2775, 2500, 1560; ^1H NMR (D_2O) δ 1.13 (d, J = 6.3 Hz, 3H), 2.99 (dd, J = 8.5, 11.8 Hz, 1H), 3.28 (dd, J = 3.1, 9.3 Hz, 1H), 3.39 (dd, J = 8.4, 12.2 Hz, 1H), 4.01 (m, 1H), 4.11 (t, J = 3.2 Hz, 1H), 4.34 (dt, J = 3.9, 8.5 Hz, 1H); ^{13}C NMR (D_2O ref DMSO) δ 20.8, 47.7, 65.5, 68.5, 71.0, 71.5. Anal. Calcd for $C_6H_{14}O_3NCl$: C, 39.2, H, 7.7, N, 7.6. Found: C, 39.1; H, 7.4; N, 7.4.

(2*R*,3*S*,4*R*,1″*R*)-2-(Hydroxyethyl)-3,4-dihydroxypyrrolidine Hydrochloride (3a·HCl). By following the same procedure described above, 50 mg (100%) of **3a·HCl** was obtained: mp 183−184 °C; $[\alpha]^{25}_D = -21.0°$ (*c* 0.50, MeOH); IR (KBr) 3600, 3100, 2930, 2815, 2450, 1550; ^1H NMR (D_2O) δ 1.14 (d, J = 6.4 Hz, 3H), 3.00 (dd, J = 8.6, 11.6 Hz, 1H), 3.26 (br d, J = 8.3 Hz, 1H), 3.43 (dd, J = 8.5, 11.9 Hz, 1H), 4.05 (m, 1H), 4.21 (t, J = 3.1 Hz, 1H), 4.33 (dt, J = 3.8, 8.5 Hz, 1H); ^{13}C NMR (D_2O ref dioxane) δ 20.5, 48.3, 64.2, 67.0, 70.8, 71.2. Anal. Calcd for $C_6H_{14}O_3NCl$: C, 39.2; H, 7.7; N, 7.6. Found: C, 38.9; H, 7.9; N, 7.3.

(2*R*,3*S*,4*R*,1″*S*)-2-[1″-Hydroxy-2″-(methoxymethoxy)-ethyl]-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (14b). By following the same procedure described above for **13a** (using $LiEt_3BH$), 200 mg (100%) of **14b** was obtained as a white foam: $[\alpha]^{25}_D = 91°$ (*c* 0.95, Cl_3CH); IR (NaCl) 3495, 2936, 1447; ^1H NMR (Cl_3CD) δ 1.23 (s, 3H), 1.60 (s, 3H), 2.62 (t, J = 5.7 Hz, 1H), 2.89 (dd, J = 6.2, 12.9 Hz, 1H), 3.16 (d, J = 13.0 Hz, 1H), 3.33 (m, 1H), 3.34 (s, 3H), 3.82 (m, 3H), 4.23 (t, J = 6.2 Hz, 1H), 4.58 (m, 1H), 4.60 (s, 2H), 7.22−7.69 (m, 13H); ^{13}C NMR (Cl_3CD) δ 24.6, 26.1, 55.2 (2C), 62.9, 69.2, 70.6, 76.7, 79.1, 82.7, 96.6, 113.1, 119.7, 120.2, 125.5, 127.0, 127.4, 127.8, 128.2, 128.5, 128.6, 140.3, 140.4, 143.0, 146.1, 148.8. Anal. Calcd for $C_{30}H_{33}O_5N$: C, 73.9; H, 6.8; N, 2.9. Found: C, 73.5; H, 7.1; N, 2.7.

(2*R*,3*S*,4*R*,1″*R*)-2-[1″-Hydroxy-2″-(methoxymethoxy)-ethyl]-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (13b). $NaBH_4$ (34 mg, 0.86 mmol, 250 mol %) was added to a solution of **11b** (167 mg, 0.34 mmol) in THF/MeOH (1/1, 6 mL) at room temperature; the resulting suspension was stirred for 20h and quenched with AcOEt (0.2 mL). The suspension was partitioned between H_2O (25 mL) and CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried, and evaporated to give a residue that was purified by column chromatography (hexanes/EtOAc 6/1) to afford both epimers in a 3/1 ratio, 120 mg (**14b**) and 40 mg (**13b**) (yield 95%); $[\alpha]^{25}_D = 199.4°$ (*c* 1.8, Cl_3CH); IR (NaCl) 3732, 2925, 1453; ^1H NMR (Cl_3CD) δ 1.15 (s, 3H), 1.43 (s, 3H), 2.58 (t, J = 7.7 Hz, 1H), 3.12 (dd, J = 6.5, 10.3 Hz, 1H), 3.25 (s, 3H), 3.31 (m, 1H), 3.57 (m, 2H), 3.77 (m, 3H), 4.44 (d, J = 6.4 Hz, 1H), 4.52 (d, J = 6.4 Hz, 1H), 4.70 (m, 1H), 7.21−7.75 (m, 13H); ^{13}C NMR (Cl_3CD) δ 24.4, 25.6, 54.2, 55.0, 61.3, 67.4, 70.3, 77.3, 81.3, 81.7, 96.6, 114.2, 119.8, 120.5, 125.1, 126.5, 127.0, 127.6, 128.0, 128.4, 128.6, 128.7, 129.3, 139.4, 141.5, 142.8, 148.1, 148.5. Anal. Calcd for $C_{30}H_{33}O_5N$: C, 73.9; H, 6.8; N, 2.9. Found: C, 74.1; H, 6.9; N, 2.9.

(2*R*,3*S*,4*R*,1″*S*)-2-(1″,2″-Dihydroxyethyl)-3,4-dihydroxypyrrolidine hydRochloride (2a·HCl). Pd/C (18 mg, 10%) and concd HCl (0.1 mL) were added to a solution of **14b** (58 mg, 0.12 mmol) in deoxygenated MeOH (2 mL). The flask was purged with argon and then evacuated (vacuum) and pressurized (H_2) three times. The reaction mixture was mechanically shaken under 52 psi of H_2 for 13 h. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was washed with toluene to give a yellow oil that was recrystallized from ethanol/ether to afford 24 mg of **2a·HCl** (100%) as a white solid: mp 146−148 °C; IR (KBr) 3300, 3100, 2940, 2800, 2450, 1550; ^1H NMR (D_2O) δ 3.03 (dd, J = 8.9, 11.9 Hz, 1H), 3.45 (dd, J = 8.9, 11.8 Hz, 2H), 3.55 (m, 2H), 3.96 (m, 1H), 4.23 (t, J = 2.6 Hz, 1H), 4.35 (dt, J = 3.8, 8.2 Hz, 1H), ^{13}C NMR (D_2O ref dioxane) δ 48.4, 63.4, 64.1, 68.4, 71.0, 71.2. Anal. Calcd for $C_6H_{14}O_4NCl$: C, 36.1; H, 7.1; N, 7.0. Found: C, 36.0; H, 6.9; N, 6.9.

(2*R*,3*S*,4*R*,1″*R*)-2-(1″,2″-Dihydroxyethyl)-3,4-dihydroxypyrrolidine Hydrochloride (2b·HCl). By following the same procedure described above, 13 mg of **2b·HCl** (100%) was obtained as a white solid: mp 168−170 °C; IR (KBr) 3390, 3090, 2935, 2755, 2460, 1578; ^1H NMR (D_2O) δ 3.02 (dd, J = 8.4, 11.5 Hz, 1H), 3.43 (m, 3H), 3.62 (dd, J = 3.1, 12.2 Hz, 1H), 3.98 (m, 1H), 4.14 (t, J = 3.6 Hz, 1H), 4.35 (dt, J = 3.9, 8.1 Hz, 1H), ^{13}C NMR (D_2O ref dioxane) δ 47.6, 64.2 (2C), 69.3, 70.9, 71.5. Anal. Calcd for $C_6H_{14}O_4NCl$: C, 36.1; H, 7.1; N, 7.0. Found: C, 36.0; H, 6.8; N, 6.8.

(2*S*,3*S*,4*R*)-2-[4″-(1,3-Dioxolanyl)-1″-oxobutyl]-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (11c). A solution of 3-(1,3-dioxolane)-1-propyl bromide (328 mg, 1.81 mmol, 250 mol %) in THF (2.9 mL) was added to a suspension of magnesium (120 mg) in THF (1 mL) over a period of 30 min at 30−35 °C. Stirring was continued for 2 h

at 35−40 °C, and then the Grignard reagent was cooled at −40 °C and a solution of **9c** (320 mg, 0.73 mmol, 100 mol %) in THF (2.9 mL) was added. Stirring was continued for 3.5 h from −40 to −5 °C. The reaction was quenched with a few drops of H_2O, and it was allowed to reach room temperature. The suspension was partitioned between H_2O (30 mL) and CH_2Cl_2 (35 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried and evaporated to give a residue that was purified by chromatography (70−230 mesh silica gel, EtOAc/hexane 1/4) to provide 358 mg (96%) of **11c** as a white foam. Recrystallization from Et_2O provided **11c** as a white solid: mp = 178−180 °C; $[\alpha]^{25}_D$ = 117.9° (*c* 1.18, Cl_3CH); IR (NaCl) 2934, 1698, 1086; ^{1}H NMR (Cl_3CD) δ 1.17 (s, 3H), 1.41 (s, 3H), 1.68 (dt, *J* = 4.8, 7.6 Hz, 2H), 2.03 (dt, *J* = 7.5, 18.0 Hz, 1H), 2.62 (dt, *J* = 7.7, 18.0 Hz, 1H), 3.37 (m, 2H), 3.49 (dd, *J* = 3.5, 12.2 Hz, 1H), 3.88 (m, 4H), 4.53 (m, 2H), 4.78 (t, *J* = 4.7 Hz, 1H), 7.09−7.72 (m, 13H); ^{13}C NMR (Cl_3CD) δ 25.1, 26.3, 27.2, 35.4, 55.3, 64.8 (2C), 70.3, 77.1, 80.1, 81.5, 103.8, 113.5, 119.8, 120.1, 125.7, 126.9, 127.4, 127.7, 127.9, 128.5 (2C), 128.8, 139.4, 141.5, 142.9, 147.1, 148.4, 208.4. Anal. Calcd for $C_{32}H_{33}O_5N$: C, 75.1; H, 6.5; N, 2.7. Found: C, 74.9; H, 6.5; N, 2.7.

(2*R*,3*S*,4*R*,1″*S*)- and (2*R*,3*S*,4*R*,1″*R*)-2-(4″-[1,3-Dioxolanyl)-1″-hydroxybutyl]-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (13c and 14c). $LiEt_3BH$ (0.90 mL, 0.90 mmol, 1.0 M in THF, 200 mol %) was added dropwise to a stirred solution of **11c** (225 mg, 0.44 mmol) in THF (3.9 mL) at 0 °C. The stirring was continued at 0 °C for 18 h, and then AcOEt (0.25 mL) was added. The reaction mixture was partitioned between H_2O (35 mL) and CH_2Cl_2 (35 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL), and the combined organic layers were dried and evaporated. The crude product was purified by chromatography (230−400 mesh silica gel, hexane/EtOAc 2/1) to afford both epimers in a 4/1 ratio, 166 mg (**13c**) and 42 mg (**14c**) (yield 92%) as a white foam. **13c**: $[\alpha]^{25}_D$ = 183.2° (*c* 0.81, Cl_3CH); IR (NaCl) 3600, 2936, 1449; ^{1}H NMR (Cl_3CD) δ 1.14 (s, 3H), 1.24 (m, 1H), 1.41 (s, 3H), 1.61 (m, 3H), 2.44 (t, *J* = 7.9 Hz, 1H), 3.29 (dd, *J* = 4.7, 14.2 Hz, 1H), 3.57 (m, 2H), 3.81 (m, 5H), 4.71 (m, 2H), 7.18−7.75 (m, 13H); ^{13}C NMR (Cl_3CD) δ 24.3, 25.6, 28.9, 29.9, 54.0, 64.4, 64.6, 64.7, 67.1, 77.3, 81.5, 81.9, 104.8, 114.1, 119.7, 120.4, 125.0, 126.5, 127.1, 127.5, 127.9, 128.4, 128.6, 128.7, 129.2, 139.4, 141.5, 142.9, 148.2, 148.6. Anal. Calcd for $C_{32}H_{35}O_5N$: C, 74.8; H, 6.9; N, 2.7. Found: C, 74.7; H, 6.9; N, 2.7. **14c**: $[\alpha]^{25}_D$ = 143.6° (*c* 0.83, Cl_3CH); IR (NaCl) 3600, 2933, 1449; ^{1}H NMR (Cl_3CD) δ 1.25 (s, 3H), 1.43 (m, 2H), 1.60 (s, 3H), 1.80 (m, 2H), 2.41 (t, *J* = 5.7 Hz, 1H), 3.05 (dd, *J* = 6.1, 13.0 Hz, 1H), 3.23 (dd, *J* = 3.1, 12.9 Hz, 1H), 3.39 (br s, 1H), 3.60 (br s, 1H), 3.92 (m, 4H), 4.23 (t, *J* = 6.3 Hz, 1H), 4.60 (m, 1H), 4.83 (t, *J* = 4.6 Hz, 1H), 7.19−7.74 (m, 13H); ^{13}C NMR (Cl_3CD) δ 24.6, 26.1, 29.2, 30.4, 55.2, 64.8, 64.8, 65.6, 70.2, 76.9, 79.3, 82.9, 104.6, 113.0, 119.6, 120.2, 125.7, 127.3, 127.4, 127.5, 127.7, 128.2, 128.4, 128.7, 139.8, 141.0, 143.4, 147.1, 148.4. Anal. Calcd for $C_{32}H_{35}O_5N{\cdot}0.25H_2O$: C, 74.2; H, 6.9; N, 2.7. Found: C, 74.1; H, 7.2; N, 2.3.

(1*S*,2*R*,8*S*,8a*R*)-1,2,8-Triacetoxyhydroindolizidine, 8-*epi*-Swainsonine Triacetate (5b). HCl (aqueous, 5%, 0.3 mL) was added to a solution of **13c** (50 mg, 0.12 mmol) in THF (1 mL). The solution was stirred at room temperature overnight. The mixture was partitioned between a solution of KH_2PO_4/NaOH (pH = 7, 10 mL) and CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated. The crude product (32 mg, 0.08 mmol) was dissolved in deoxygenated MeOH (1 mL), and Pd/C (10 mg, 30 wt %, 10%) was added. The flask was purged with argon and then evacuated (vacuum) and pressurized (H_2) three times. The reaction mixture was mechanically shaken under 52 psi of H_2 for 3 h, and AcOH (0.1 mL) was added (to obtain pH = 5) and hydrogenated for 36 h at 52 psi. The catalyst was removed by filtration, and the filtrate was evaporated. The residue was washed with toluene to give a yellow oil that was acetylated using Ac_2O (1 mL), DMAP (cat.), and pyridine (1 mL) during 48 h at room temperature. A few drops of saturated $NaHCO_3$ solution were added to the reaction mixture, which was partitioned between $NaHCO_3$ solution (5 mL) and Cl_3CH (2 × 10 mL). The combined organic layers were washed consecutively with saturated $CuSO_4$ solution (2 × 10 mL) and H_2O (2 × 10 mL), dried, and concentrated. The residue was purified by flash chromatography (Cl_3CH/MeOH 2%) to give 15 mg (94%) of **5b**: $[\alpha]^{25}_D$ = −17.4° (*c* 0.80, Cl_3CH); ^{1}H NMR (Cl_3CD) δ 1.18−2.28 (m, 6H), 2.03 (s, 3H), 2.05 (s, 3H), 2.14 (s, 3H), 2.43 (dd, *J* = 6.6 Hz, 11.0 Hz, 1H), 3.24 (m, 2H), 5.23−5.43 (m, 3H); ^{13}C NMR (Cl_3CD) δ 19.6, 20.5, 20.7, 21.5, 29.6, 53.1, 59.0, 66.1, 66.6, 69.8, 71.9, 170.1, 170.3 (2C).

(2*S*,3*S*,4*R*)-2-(2″-Fluoro-1″-oxoethyl)-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (11d). A solution of **11a** (145 mg, 0.336 mmol) in THF (4.5 mL) was added dropwise to a stirred solution of NaHMDS (0.5 mL, 0.5 mmol, 150 mol %, 1.0 M in THF) in THF (0.9 mL) at −78 °C; the resulting solution was stirred for 1.5 h at −78 °C, and then this solution was added via cannula to a precooled (−78 °C) solution of $(PhSO_2)_2NF$ (170 mg, 0.54 mmol, 160 mol %) in THF (3 mL). The resulting mixture was stirred at −78 °C for 3 h and quenched with saturated NH_4Cl solution. The suspension was partitioned between H_2O (15 mL) and CH_2Cl_2 (2 × 25 mL). The organic layer was washed with brine, dried, and evaporated to afford a residue, which was purified by chromatography (hexanes/EtOAc 6/1) to give 87 mg (60%) of **11d**, 37 mg (26%) of **11a**, and 7 mg (5%) of the corresponding difluoro compound: $[\alpha]^{22}_D$ = 143.8 (*c* 0.53, Cl_3CH); IR (NaCl) 2936, 1744, 1449; ^{1}H NMR (Cl_3CD) δ 1.20 (s, 3H), 1.44 (s, 3H), 3.45 (m, 3H), 4.65 (m, 4H), 7.15−7.75 (m, 13H); ^{13}C NMR (Cl_3CD) δ 25.0, 26.1, 55.0, 67.9, 76.9, 80.1, 81.0, 84.9 (d, *J* = 182.5 Hz), 113.6, 119.9, 120.3, 125.9, 126.8, 127.4, 127.6, 127.9, 128.0, 128.6, 128.8, 129.0, 139.5, 141.7, 142.4, 146.3, 148.1, 204.2 (d, *J* = 17.5 Hz). Anal. Calcd for $C_{28}H_{26}O_3NF{\cdot}2H_2O$: C, 70.1; H, 6.3; N, 2.9. Found: C, 70.2; H, 6.6; N, 2.5. Difluoro compound: $[\alpha]^{22}_D$ = 78.6° (*c* 1.31, Cl_3CH); IR (NaCl) 3068, 1763, 1490, 1449; ^{1}H NMR (Cl_3CD) δ 1.14 (s, 3H), 1.34 (s, 3H), 3.27 (dd, *J* = 6.0 Hz, 12.5 Hz, 1H), 3.44 (dd, *J* = 3.7, 12.5 Hz, 1H), 3.79 (d, *J* = 7.5 Hz, 1H), 4.57 (m, 2H), 5.26 (t, *J* = 53.7 Hz, 1H), 7.10−7.73 (m, 13H); ^{13}C NMR (Cl_3CD) δ 25.1, 25.8, 54.6, 66.6, 76.8, 80.5, 81.2, 109.3 (t, *J* = 252.5 Hz), 114.2, 119.8, 120.1, 120.3, 124.8, 125.5, 125.9, 127.0, 127.2, 127.4, 127.6, 127.9, 128.1, 128.2, 128.4, 128.6, 128.7, 129.0, 129.1, 139.5, 139.7, 141.5, 142.4, 143.4, 146.7, 148.0, 150.7, 197.0 (t, *J* = 25.0 Hz).

(2*R*,3*S*,4*R*,1″*S*)-2-(2″-Fluoro-1″-hydroxyethyl)-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (14d). The ketone **11d** was reduced with K-Selectride following the same procedure as used for **11a**. The crude product was purified by chromatography (70−230 mesh silica gel, hexane/EtOAc 4/1) to give 190 mg (95%) of **14d** as a white foam: $[\alpha]^{25}_D$ = 283.1° (*c* 0.65, Cl_3CH); IR (NaCl) 3491, 2956, 1449; ^{1}H NMR (Cl_3CD) δ (500 MHz) 1.23 (s, 3H), 1.58 (s, 3H), 2.60 (t, *J* = 6.2 Hz, 1H), 3.06 (dd, *J* = 6.4, 13.3 Hz, 1H), 3.21 (dd, *J* = 3.2, 13.3 Hz, 1H), 3.85 (m, 2H), 4.12 (m, 1H), 4.24 (ddd, *J* = 47.9, 6.4, 9.3 Hz, 1H), 4.61 (m, 1H), 4.65 (ddd, *J* = 48.8, 9.4, 5.2 Hz, 1H), 7.09−7.71 (m, 13H); ^{13}C NMR (Cl_3CD) δ 24.5, 25.9, 55.1, 62.1 (d, *J* = 4.6 Hz), 69.0 (d, *J* = 18.6 Hz), 76.9, 79.7, 82.9, 85.5 (d, *J* = 171.0 Hz), 113.5, 119.9, 120.4, 125.4, 126.9, 127.1, 127.5, 127.7, 127.9, 128.4, 128.7, 128.9, 140.1, 140.8, 142.9, 146.6, 148.5. Anal. Calcd for $C_{28}H_{28}O_3NF.3.25H_2O$: C, 66.7; H, 6.9; N, 2.8. Found: C, 66.8; H, 6.5; N, 2.4.

(2*R*,3*S*,4*R*,1″*R*)-2-(2″-Fluoro-1″-hydroxyethyl)-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (13d). $NaBH_4$ (15 mg, 0.38 mmol, 250 mol %) was added to a solution of **11d** (70 mg, 0.15 mmol) in THF/MeOH (1/1, 1 mL) at room temperature; the resulting suspension was stirred overnight and quenched with a few drops of H_3PO_4 solution (10%). The suspension was partitioned between H_2O (10 mL) and CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried, and evaporated to give a residue that was purified by column chromatography (hexanes/EtOAc 6/1) to afford both epimers in a 2/1 ratio, 41 mg (**14d**) and 19 mg (**13d**) (yield 90%): $[\alpha]^{25}_D$ = 212.5° (*c* 0.4, Cl_3CH); IR (NaCl) 3590, 2990, 1456; ^{1}H NMR (Cl_3CD) δ 1.18 (s, 3H), 1.45 (s, 3H), 2.60 (t, *J* = 7.8 Hz, 1H), 3.32 (dd, *J* = 4.6, 14.2 Hz, 1H), 3.59 (dd, *J* = 7.0, 14.2 Hz, 1H), 3.84 (m, 3H), 4.09 (ddd, *J* = 48.2,

9.4, 5.7 Hz, 1H), 4.44 (ddd, J = 47.2, 9.4, 1.7 Hz, 1H), 4.72 (dt, J = 4.7, 7.1 Hz, 1H), 7.22−7.78 (m, 13H); ^{13}C NMR (Cl_3CD) δ 24.4, 25.6, 54.3, 60.4 (d, J = 10.0 Hz), 67.4 (d, J = 18.2 Hz), 77.3, 81.1, 81.6, 85.6 (d, J = 169.5 Hz), 114.2, 119.9, 120.6, 125.1, 126.3, 127.0 (2C), 127.7, 128.0, 128.5, 128.8 (2C), 129.4, 139.4, 141.5, 142.7, 147.8, 148.3. Anal. Calcd for $C_{28}H_{28}O_3NF\cdot0.5H_2O$: C, 74.0; H, 6.4; N, 3.1. Found: C, 73.8; H, 6.4; N, 3.0.

(2*R*,3*S*,4*R*,1″*S*)-2-(2″-Fluoro-1″-hydroxyethyl)-3,4-dihydroxypyrrolidine Hydrochloride (4a·HCl). By following the same procedure as **13a**, **14d** afforded 16 mg (100%) of **4a·HCl** as a white solid: mp 168−170 °C; $[\alpha]^{22}_D$ = 62.8° (*c* 0.5, MeOH); IR (KBr) 3600, 3285, 2690, 1550, 1100; ^{1}H NMR (MeOD-d_4) δ 3.19 (m, 1H), 3.58 (m, 2H), 4.36 (m, 2H), 4.47 (br s, 1H), 4.60 (dd, J = 4.4, 47.2 Hz, 2H); ^{13}C NMR (MeOD-d_4) δ 48.7, 63.8 (d, J = 4.1 Hz), 66.9 (d, J = 20.4 Hz), 71.5 (2C), 85.6 (d, J = 170.4 Hz). Anal. Calcd for $C_6H_{13}O_3NClF\cdot1.5H_2O$: C, 31.5; H, 7.1; N, 6.1. Found: C, 31.6; H, 7.0; N, 6.1.

(2*R*,3*S*,4*R*,1″*R*)-2-(2″-Fluoro-1″-hydroxyethyl)-3,4-dihydroxypyrrolidine Hydrochloride (4b·HCl). By following the same procedure as described above, 20 mg (100%) of **4b·HCl** was obtained as a white solid: mp 140−143 °C; $[\alpha]^{25}_D$ = −8.0° (*c* 0.4, MeOH); IR (KBr) 3600, 3387, 2700, 2450, 1560, 1090; ^{1}H NMR (MeOD-d_4) δ 3.10 (m, 1H), 3.55 (m, 2H), 4.15 (m, 2H), 4.27 (br s, 1H), 4.53 (br d, J = 49.0 Hz, 2H); ^{13}C NMR (MeOD-d_4) δ 48.5, 65.1 (d, J = 6.1 Hz), 71.4 (d, J = 20.5 Hz), 72.1 (2C), 86.0 (d, J = 179.0 Hz). Anal. Calcd for $C_6H_{13}O_3NClF$: C, 35.7; H, 6.5; N, 7.0. Found: C, 35.6; H, 6.5; N, 6.9.

***O*-Methylmandelates of (2*R*,3*S*,4*R*,1″*R*)-2-(2″-Fluoro-1″-hydroxyethyl)-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (15d).** (*R*)-*O*-Methylmandelic acid (9 mg, 0.06 mmol, 110 mol %) was added to a white suspension prepared by slow addition of oxalyl chloride (5 μL, 0.06 mmol, 100 mol %) to DMF (6 μL, 0.08 mmol, 135 mol %) in acetonitrile (0.5 mL) at 0 °C. After 10 min, a solution of **13d** (25 mg, 0.06 mmol) in pyridine (0.15 mL) was added slowly, and the resultant mixture was stirred at 0 °C for 2.5 h. The pale yellow reaction mixture was diluted with ether (20 mL), the organic layer was washed twice with saturated aqueous cupric sulfate solution (2 × 5 mL) and dried over sodium sulfate, and the solvent was removed in vacuo to give a yellow oil. Purification by chromatography (silica 70−230 mesh, hexanes/AcOEt, 3/1) gave 28 mg (85%) of (*R*)-**15d** as a white foam: $[\alpha]^{22}_D$ = 43.5° (*c* 0.92, Cl_3CH); IR (NaCl) 2940, 1757, 1453; ^{1}H NMR (Cl_3CD) δ 1.20 (s, 3H), 1.53 (s, 3H), 2.76 (t, J = 6.5 Hz, 1H), 2.88 (dd, J = 6.2, 12.9 Hz, 1H), 3.17 (dd, J = 3.4, 13.0 Hz, 1H), 3.40 (s, 3H), 4.04 (t, J = 6.0 Hz, 1H), 4.49 (m, 3H), 4.70 (s, 1H), 5.00 (m, 1H), 7.23−7.72 (m, 18H); ^{13}C NMR (Cl_3CD) δ 24.9, 26.4, 55.6, 57.3, 61.3 (d, J = 8.1 Hz), 73.5 (d, J = 20.2 Hz), 77.2, 78.9, 81.4, 82.7, 83.4 (d, J = 169.3 Hz), 112.8, 120.0, 120.4, 125.6, 127.0, 127.2, 127.4, 127.5, 127.8, 127.9, 128.5, 128.6, 128.7, 128.8, 136.4, 140.2, 140.9, 143.6, 146.7, 148.6, 169.8. By following the same procedure using (*S*)-*O*-methylmandelic acid, 24 mg (89%) of (*S*)-**15d** was obtained as a white foam: $[\alpha]^{25}_D$ = 103.3° (*c* 0.9, Cl_3CH); IR (NaCl) 2937, 1760, 1453; ^{1}H NMR (Cl_3CD) δ 1.09 (s, 3H), 1.50 (s, 3H), 2.44 (t, J = 5.0 Hz, 1H), 2.80 (dd, J = 6.4, 12.5 Hz, 1H), 3.08 (dd, J = 3.8, 12.4 Hz, 1H), 3.33 (s, 3H), 3.48 (t, J = 5.7 Hz, 1H), 4.21 (m, 1H), 4.67 (s, 1H), 4.72 (m, 3H), 7.21−7.76 (m, 18H); ^{13}C NMR (Cl_3CD) δ 25.0, 26.7, 56.2, 57.2, 62.2 (d, J = 8.9 Hz), 74.6 (d, J = 21.4 Hz), 77.0, 77.9, 80.8, 82.4, 83.5 (d, J = 166.9 Hz), 112.1, 119.9, 120.2, 120.5, 125.7, 127.0, 127.3, 127.5, 127.6, 127.7, 128.0, 128.5, 128.6, 128.6, 128.8, 129.3, 136.7, 139.9, 141.4, 143.2, 146.5, 147.4, 169.6. Anal. Calcd for $C_{37}H_{36}O_5NF$: C, 74.8; H, 6.1; N, 2.4. Found: C, 74.5; H, 6.2; N, 2.1.

***O*-Methylmandelates of (2*R*,3*S*,4*R*,1″*S*)-2-(1″-Hydroxyethyl)-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (15a).** The alcohol **13a** was treated with (*S*)-*O*-methylmandelic acid and (*R*)-*O*-methylmandelic acid, following the same procedure described above to afford 52 mg (96%) of (*S*)**15a** as a white foam: $[\alpha]^{25}_D$ = 153.0° (*c* 1.05, Cl_3CH); IR (NaCl) 2938, 1744, 1451; ^{1}H NMR (Cl_3CD) δ 1.13 (s, 3H), 1.21 (d, J = 6.1 Hz, 3H), 1.50 (s, 3H), 2.49 (t, J = 6.7 Hz, 1H), 2.99 (dd, J = 6.7, 13.0 Hz, 1H), 3.12 (dd, J = 4.4, 13.0 Hz, 1H), 3.34 (s, 3H), 3.79 (t, J = 6.3 Hz, 1H), 4.38 (m, 1H), 4.63 (s, 1H), 4.79 (m, 1H), 7.18−7.69 (m, 18H); ^{13}C NMR (Cl_3CD) δ 17.7, 25.0, 26.6, 55.5, 57.1, 63.8, 71.2, 77.1, 79.0, 82.0, 82.7, 112.6, 119.7, 120.1, 125.3, 127.1, 127.2, 127.4, 127.6, 127.8, 128.2, 128.4, 128.5, 128.5, 128.6, 136.5, 139.7, 140.8, 143.7, 148.6, 169.7. Anal. Calcd for $C_{37}H_{37}O_5N.0.5H_2O$: C, 76.0; H, 6.6; N, 2.4. Found: C, 75.7; H, 6.5; N, 2.4. The corresponding compound (*R*)-**15a** was obtained (82%) as a white foam: $[\alpha]^{25}_D$ = −5.19° (*c* 1.08, Cl_3CH); IR (NaCl) 1756, 1455; ^{1}H NMR (Cl_3CD) δ 0.96 (d, J = 6.1 Hz, 3H), 1.19 (s, 3H), 1.55 (s, 3H), 2.61 (dd, J = 5.7, 8.0 Hz, 1H), 2.69 (dd, J = 6.3, 12.8 Hz, 1H), 3.07 (dd, J = 3.2, 12.9 Hz, 1H), 3.33 (s, 3H), 4.05 (t, J = 6.4 Hz, 1H), 4.42 (dt, J = 3.2, 6.7 Hz, 1H), 4.50 (s, 1H), 5.08 (m, 1H), 7.19−7.69 (m, 18H); ^{13}C NMR (Cl_3CD) δ 18.0, 25.0, 26.3, 55.3, 56.9, 65.4, 70.9, 76.9, 78.6, 81.9, 82.0, 112.6, 119.7, 120.0, 125.3, 126.3, 127.2, 127.2, 127.5, 127.5, 128.1, 128.3, 128.4, 128.5, 128.5, 136.5, 139.5, 140.8, 144.4, 146.2, 150.1, 169.1. Anal. Calcd for $C_{37}H_{37}O_5N.0.5H_2O$: C, 76.0; H, 6.6; N, 2.4. Found: C, 76.0; H, 6.4; N, 2.2.

***O*-Methylmandelates of (2*R*,3*S*,4*R*,1″*R*)-2-[1″-Hydroxy-2″-(methoxymethoxy)ethyl]-3,4-(isopropylidenedioxy)-*N*-(9′-phenylfluoren-9′-yl)pyrrolidine (15b).** By following the same procedure, (*S*)-**15b** (88%) was obtained as a white foam from **13b**: $[\alpha]^{25}_D$ = 105.8° (*c* 1.7, Cl_3CH); IR (NaCl) 2999, 1756, 1452; ^{1}H NMR (Cl_3CD) δ 1.09 (s, 3H), 1.48 (s, 3H), 2.57 (dd, J = 6.0, 7.4 Hz, 1H), 3.08 (dd, J = 6.8, 13.2 Hz, 1H), 3.13 (dd, J = 5.4, 13.2 Hz, 1H), 3.28 (s, 3H), 3.35 (s, 3H), 3.56 (t, J = 6.2 Hz, 1H), 3.68 (dd, J = 7.7, 11.3 Hz, 1H), 3.87 (d, J = 10.6 Hz, 1H), 4.33 (c, J = 6.4 Hz, 1H), 4.43 (d, J = 6.6 Hz, 1H), 4.46 (d, J = 6.5 Hz, 1H), 4.71 (s, 1H), 4.89 (t, J = 7.3 Hz, 1H), 7.17−7.71 (m, 18H); ^{13}C NMR (Cl_3CD) δ 25.0, 26.7, 55.1, 55.8, 57.2, 61.2, 68.1, 74.3, 77.5, 79.3, 81.6, 82.9, 96.5, 112.9, 119.9, 120.2, 125.5, 127.1, 127.2, 127.4, 127.7, 127.8, 127.9, 128.4, 128.5, 128.6, 128.8, 136.8, 139.7, 141.5, 143.6, 147.5, 148.5, 169.9. Anal. Calcd for $C_{39}H_{40}O_7N$: C, 73.8; H, 6.4; N, 2.2. Found: C, 73.5; H, 6.6; N, 2.1. (*R*)-**15b** (85%): $[\alpha]^{25}_D$ = 27.8° (*c* 1.0, Cl_3CH); IR (NaCl) 2934, 1752, 1452; ^{1}H NMR (Cl_3CD) δ 1.18 (s, 3H), 1.52 (s, 3H), 2.78 (dd, J = 6.1, 8.7 Hz, 1H), 3.01 (s, 3H), 3.05 (dd, J = 7.1, 13.4 Hz, 1H), 3.24 (dd, J = 13.4, 3.8 Hz, 1H), 3.38 (dd, J = 6.2, 11.3 Hz, 1H), 3.44 (s, 3H), 3.49 (d, J = 9.7 Hz, 1H), 3.96 (t, J = 7.3 Hz, 1H), 3.96 (d, J = 6.6 Hz, 1H), 4.00 (d, J = 6.5 Hz, 1H), 4.52 (m, 1H), 4.74 (s, 1H), 5.14 (t, J = 6.5 Hz, 1H), 7.21−7.70 (m, 18H); ^{13}C NMR (Cl_3CD) δ 24.8, 26.2, 54.8, 55.0, 57.2, 60.8, 68.3, 72.9, 77.5, 78.0, 81.9, 82.7, 96.4, 113.4, 119.8, 120.2, 125.4, 127.0, 127.2, 127.3, 127.3, 127.6, 127.7, 128.0, 128.5, 128.7, 136.7, 140.2, 140.8, 144.0, 147.6, 149.6, 169.7. Anal. Calcd for $C_{39}H_{40}O_7N$: C, 73.8; H, 6.4; N, 2.2. Found: C, 73.5; H, 6.6; N, 2.1.

Acknowledgment. We thank the CICYT (Spain, Grant No. SAF93-0767) and the Xunta de Galicia (Grant No. XUGA20908B94) for financial support. M.J.B. thanks the Xunta de Galicia (Spain) for a fellowship. We thank Prof. Rafael Suau (University of Málaga, Spain) for the elemental analyses.

JO9604245