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Formal Enantiospecific Synthesis of (+)-FR900482

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The enantiospecific synthesis of FK973, and thus a formal enantiospecific synthesis of the antitumor antibiotic (+)-FR900482, is reported. Addition of aniline **8** to chiral epoxide **9**, prepared from L-vinylglycine, afforded amino alcohol **12**. After protection of the aliphatic nitrogen with the 9-phenylfluoren-9-yl group, to preserve the acidic stereocenter from racemization, formation of the aziridine **14** and intramolecular condensation under basic conditions gave azocinone **15**. Hydroxymethylation at the benzylic position was achieved by a process involving methylenation, epoxidation, and hydrogenolysis; the absolute stereochemistry of the resulting alcohol **23** was determined by X-ray crystallographic analysis. The hydroxyl group of **23** was carbamoylated, and the aromatic amine was deprotected electrochemically and then oxidized to give an unstable hydroxylamine that was immediately protected as acetate **26**. Oxidation of **26** with DMP, followed by hydrazinolysis of the acetyl group led to spontaneous closure of the resulting *N*-hydroxyamino ketone to hemiketal **28**, which can be considered as a fully protected precursor of FR900482 and derivatives. Acid treatment to remove the protecting groups and acetylation afforded the triacetate FK973.

Introduction

FR900482 (**1**) and its dihydro derivative FR66979 (**2**) are two potent antitumor agents isolated from *Streptomyces sandaensis* No. 6897.[1,2] These compounds possess an unusual hydroxylamine hemiketal functionality and appear as a mixture of diastereoisomers in equilibrium via **5**. Form A is favored in neutral or acidic conditions, probably as the result of an intramolecular hydrogen bond between the aziridine NH and the bridging hydroxylamine oxygen. Both compounds show promising antitumor activity,[3] equal to or greater than that of the structurally related mitomycin C (**6**), a compound widely used in cancer therapy. Intensive studies to define the mechanisms of their biological activity[4] have shown that reductive activation of FR900482 and FR66979 leads to an electrophilic, mitosene-like intermediate that, like the mitomycins, forms interstrand DNA−DNA cross-links.[5] Other members of this family, FK973 (**3**)[6] and FK317 (**4**),[7] were obtained by chemical modification of FR900482 in an effort to develop new drugs with reduced side effects and stronger antitumor activity. The triacetate **3** is also isolated as a mixture of isomers, but with form B predominant (7:79 ratio). This derivative is less toxic and approximately three times more potent than mitomycin C against a variety of tumor cells in mice.[6a] Potent antitumor activity has recently been reported for FK317 (**4**) as well, and successful phase I clinical trials make it the most promising drug candidate in this family. These semisynthetic derivatives also form interstrand DNA−DNA and DNA−protein cross-links after being bioactivated in cells.

The unique structure and promising antitumor activities have made these compounds attractive synthetic

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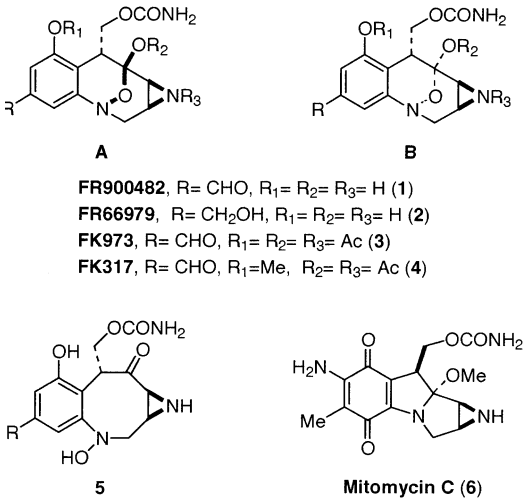

FIGURE 1.

targets for many research groups;[8] many approaches[9] have been described, but only two total syntheses[10] of racemic FR900482, one of the enantiomerically pure material,[11] and a formal enantioselective synthesis[12] have been reported to date. We report herein our contribution to this field by presenting the enantiospecific synthesis of FK973, which can be considered a formal enantiospecific synthesis of the natural product FR900482.[13]

Results and Discussion

Our synthetic approach involved intermolecular coupling of a suitably protected aniline (**8**) with a chiral epoxide (**9**) (see Figure 2) followed by intramolecular condensation to form the aziridinobenzoazocinone ring enantiospecifically. We considered compound **15** to be the key intermediate for synthesis of FR900482 and conge-

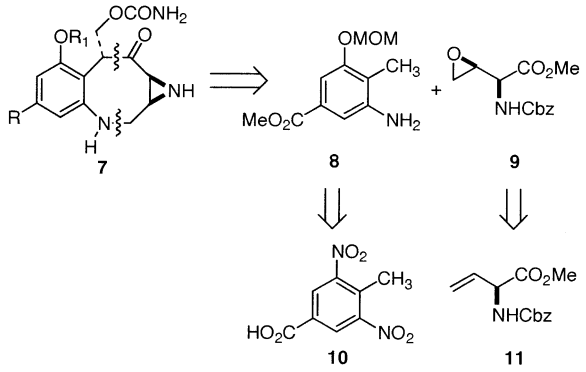

FIGURE 2.

ners. The aromatic precursor, **8**, was easily prepared on large scale from commercially available 3,5-dinitro-*p*-toluic acid following literature procedures.[9a,14] The precursor to the aliphatic portion of the molecule was prepared from L-methionine methyl ester hydrochloride following the published procedure for the synthesis of *N*-Cbz-L-vinylglycine methyl ester (**11**).[15] Epoxidation of **11** with an excess of *m*-CPBA gave a 1/4 ratio of anti and syn isomers of epoxide **9**.[15a,16] Although complete separation of the two isomers of **9** can be achieved by preparative HPLC, we decided to carry the mixture on and perform the separation by column chromatography at a later stage.

The amino alcohol **12** (Scheme 1) was obtained in 90% yield by regioselective ring-opening[17] of epoxide **9** with aniline **8** in CH_3CN in the presence of $Mg(ClO_4)_2$. To preserve the enantiomeric purity of the product through the next steps in the synthesis, we needed a protecting group on the aliphatic nitrogen able to inhibit deprotonation α to the carbonyl group; for this purpose **12** was transformed in its *N*-(9-phenylfluoren-9-yl) derivative.[18] Hydrogenolysis of the Cbz group to free the amine was followed by treatment with PfBr in the presence of K_3PO_4 and $Pb(NO_3)_2$ to give a mixture of *N*,*N*-diPf (major component) and *N*-monoPf (**13**); the mixture was converted into **13** alone by refluxing in MeOH in the presence of a catalytic amount of 1 M HCl in 82% overall yield (1:5 mixture of epimers as determined by ^1H NMR). Cyclization to the aziridine ring and protection of the aromatic amine occurred in the same step when **13** was treated with freshly prepared benzenesulfonic anhydride (Bs_2O) in pyridine. At this point, we were able to separate the syn isomer cleanly from the anti diastereomer, isolating **14** in 76% yield. Deprotonation at the benzylic position with KHMDS in THF and intramolecular condensation of the resulting carbanion with the aziridino methyl ester afforded the eight-membered ring **15** in 72% yield.

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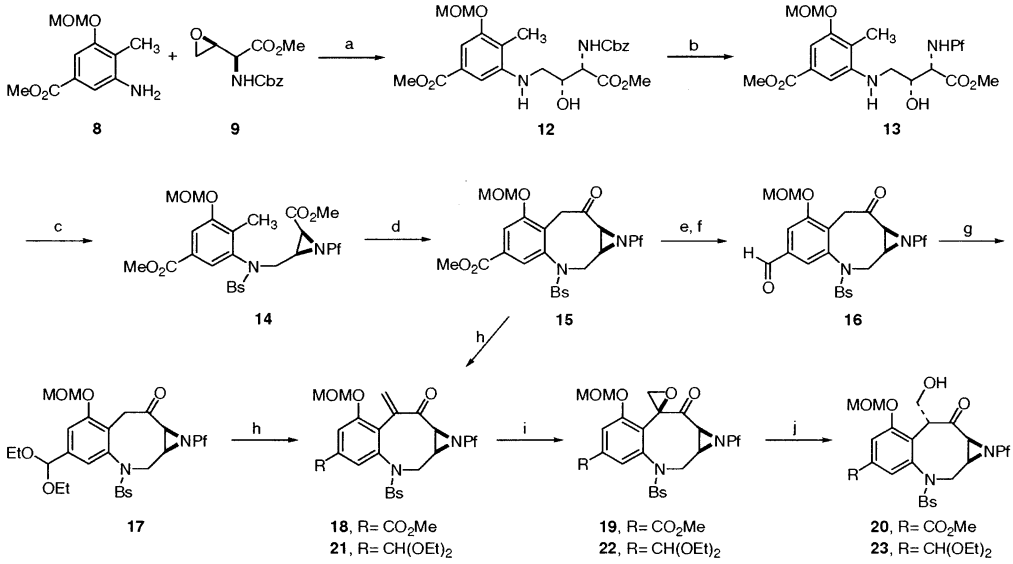
SCHEME 1[a]



[a] Reagents: (a) $Mg(ClO_4)_2$, CH_3CN (90%). (b) (i) H_2, Pd−C, (ii) PfBr, (iii) MeOH, cat. HCl (82%). (c) Bs_2O (76%). (d) KHMDS (72%). (e) $LiAlH_4$, THF (97%). (f) $(COCl)_2$, DMSO, Et_3N (94%). (g) $HC(OEt)_3$, *p*-TsOH (93%). (h) $(H_2CO)_n$, Triton B (97%). (i) H_2O_2, TBAF (80%, **19**) or TBHP, Triton B (77%, **22**). (j) H_2, Pd−C, Py (90%).

Hydroxymethylation of **15** was more difficult than expected. Alkylation of the enolate generated by treatment with bases such as KHMDS, LDA, NaH, or Triton B followed by addition of an electrophile (SEMCl, BOMCl, *p*-formaldehyde, or trioxane) afforded mainly *O*-alkylated products. Trapping the enolate with TBSCl and then treating it with TBAF followed by SEMCl failed, as did aldol-type condensations of the enol silyl ether with dibenzyloxymethane catalyzed by TMSOTf,[19] or reactions using Mukaiyama's conditions.[20] Also unsuccessful was direct condensation with formaldehyde and LiOH in THF/H_2O.[10a] Nevertheless, when **15** was treated with *p*-formaldehyde and Triton B,[21] some hydroxymethylated product **20** was isolated. Unfortunately, although a number of variations in concentration, temperature, time, and base were explored in attempts to increase the yield, enone **18** was always the main product. When the reaction was performed at 65 °C for 1 h using Triton B as base, **18** was isolated in almost quantitative yield (97%). Since elimination of water under the reaction conditions proved to be so facile, we decided to investigate the possibility of functionalizing the enone to obtain the desired alcohol **20**.

1,4-Addition of oxygenated nucleophiles[22] (KOAc, NaOBn) to the enone **18** and the alkoxymercuration reaction[23] with benzyl alcohol as the nucleophile both failed to functionalize the enone at the 4-position. Epoxidation of **18** with *tert*-butyl hydroperoxide (TBHP) or H_2O_2 was then explored, with the best result obtained with H_2O_2 and TBAF as the base in DMSO[24] (80% yield of **19**, 89% based on recovered starting material). For the reduction of α,β-epoxyketones to β-hydroxyketones, several methods and reagents have been reported. Although treatment with PhSeNa[25] or NaI/NaOAc[26] were unsuccessful, better results were obtained by using SmI_2[27] in a 2:1 mixture of THF:MeOH, which afforded alcohol **20** in 63% yield. Attempts to increase the yield of **20** were fruitless, with the enone elimination product again forming as the main side product. As an alternative, we investigated catalytic hydrogenolysis for reduction of epoxide **19** to the desired alcohol **20**. Hydrogenation of **19** in MeOH with Pd/C as the catalyst gave a complex mixture, but we observed that the addition of some inorganic salts slowed the reduction process and made it more selective. Finally, we found that by adding pyridine to the reaction mixture, we could isolate the hydroxymethyl derivative **20** in 92% yield.

At this point, we reconsidered our synthetic strategy and thought it more convenient to reduce the aromatic ester to the corresponding aldehyde oxidation level of the final target before undertaking the hydroxymethylation sequence. LAH reduction of **15** in THF gave a diol (97%), which was oxidized to the keto aldehyde **16** under Swern conditions[28] in 94% yield. The aldehyde could be protected selectively as the diethyl acetal **17** in 93% yield by treatment with triethyl orthoformate in THF/ethanol in the presence of *p*-TsOH. The diethyl acetal was chosen over the dimethyl analogue since we encountered solubility problems with the latter derivative.

Reaction of ketone **17** with *p*-formaldehyde and Triton B afforded enone **21** in 97% yield. The best conditions for the epoxidation of **18** did not apply to acetal **21**,

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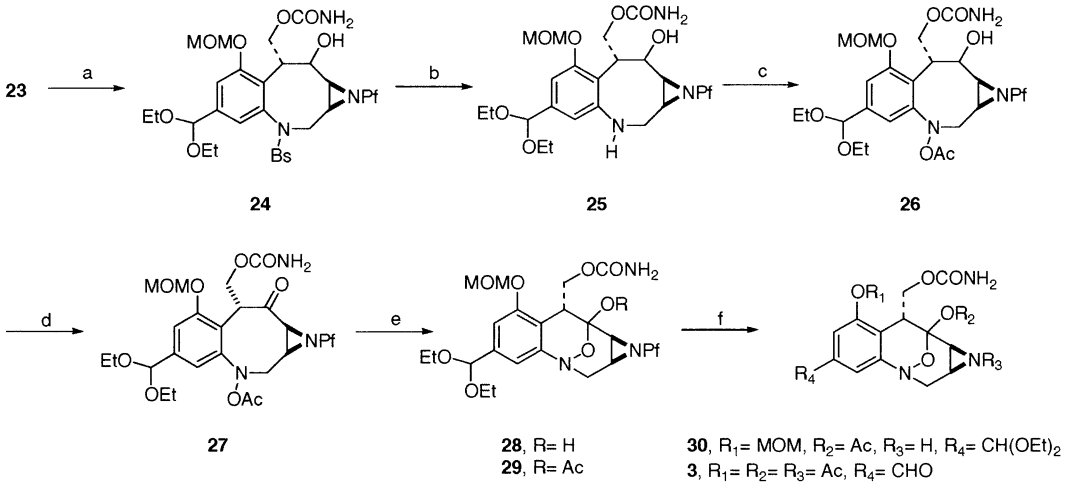
SCHEME 2[a]



[a] Reagents: (a) (i) $Cl_3CCONCO$, (ii) $NaBH_4$ (80%). (b) $2e^-$ (91%). (c) (i) Davis' oxaziridine (63%), (ii) Ac_2O, NaOAc (92%). (d) DMP (91%). (e) NH_2NH_2 (97%). (f) (i) TFA, Et_3SiH. (ii) Ac_2O, Py (52%).

because the reaction became extremely slow. However, upon treatment with TBHP and Triton B[29] a mixture of epoxides was obtained, the major one being isolated in 77% yield (**22**). The minor epoxide was easily recycled to enone **21** by treatment with SmI_2 in THF (82% yield). Catalytic hydrogenation of **22** was again successfully applied to give **23** in 90% isolated yield. Interestingly, hydrogenolysis of the benzylic acetal was not observed and the overreduction of the hydroxymethyl group to methyl (observed when $NaHCO_3$[30] was added to the reaction mixture) was again avoided by using pyridine. The stereochemistry of **23** was determined unambiguously by X-ray crystallography.[31]

Carbamoylation of **23** was achieved by treatment with trichloroacetyl isocyanate[32] at 0 °C, followed by addition of a solution of NH_3 in methanol (65% yield). When electrolysis was applied to remove the benzenesulfonyl group of the resulting ketocarbamate, the main product isolated was enone **21**. To prevent base-induced[33] elimination of the carbamate, the ketone was reduced first, to give alcohol **24** (Scheme 2) in which there is no center sensitive to base. Treatment of **23** with trichloroacetyl isocyanate[32,34] in THF followed by reduction with $NaBH_4$ in EtOH gave **24** in 80% yield. The benzenesulfonyl group was now reduced electrochemically[35] and **25** was isolated in 91% yield. Oxidation of the amine to hydroxylamine was attempted with *m*-CPBA and MMPP[36] under different conditions, but only with Davis' oxaziridine[37] was the yield acceptable (63%). Immediately, the unstable hydroxylamine was selectively protected with Ac_2O/NaOAc to give acetoxyamine **26** in 92% yield. Oxidation of the hydroxyl group of **26** to the ketone under Swern conditions, PDC or P_2O_5/DMSO failed, resulting mainly in the recovery of starting material. The Dess−Martin periodinane (DMP)[38] in CH_2Cl_2 was much more effective, affording keto-carbamate **27** in 91% yield.

Removal of the four different protecting groups was the only task remaining. Hydrolysis of the *N*-OAc group was easily accomplished with hydrazine in a 1:1 mixture of CH_2Cl_2:MeOH to give spontaneously the hemiacetal **28** in almost quantitative yield. Finally, **28** was converted into FK973 with TFA:CH_2Cl_2 in the presence of Et_3SiH, followed by acetylation with Ac_2O in pyridine. The product obtained was compared with a sample of authentic FK973, prepared by treatment of natural FR90-0482 with acetic anhydride/pyridine,[1a] showing identical properties (TLC, spectroscopic data).

The utility of this synthetic route rests on the relevance of **28** as a precursor to every member of the FR900482 family by careful manipulation of the protected functional groups. Several selective deprotection methods were also investigated with acetate **29**, obtained from **28** by treatment with Ac_2O and DMAP in pyridine. The most interesting result was the selective removal of the phenylfluorenyl group, which was cleanly achieved by reduction of **29** with sodium naphthalenide in DME to give **30** (95% yield after column chromatography). This result suggests that this synthetic protocol could also be applied to the synthesis of FK317, starting with an aniline in which the phenolic hydroxyl is protected as a methyl[39] instead of methoxymethyl ether. In summary, a formal enantiospecific synthesis of the antitumor antibiotic (+)-

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FR900482 has been developed[13] in a convergent manner from aniline **8** and methyl (2*S*,3*S*)-2-[(benzyloxycarbonyl)amino]-3,4-epoxybutanoate.

Experimental Section

Methods and Materials. All reactions requiring anhydrous conditions were conducted in flame-dried glassware under an atmosphere of argon. Solvents were distilled immediately before use: THF and Et_2O from Na/benzophenone; CH_2Cl_2, DMSO, benzene, pyridine, and Et_3N from CaH_2; and MeOH from $Mg(OCH_3)_2$. CH_3CN was distilled first from P_2O_5 and then from CaH_2. K_3PO_4 and $Pb(NO_3)_2$ were dried in a muffle furnace at 250 °C and cooled in a desiccator under nitrogen before use. Tetraethylammonium bromide (TEAB) was recrystallized four times from absolute EtOH and dried overnight in a Kugelrohr oven at 100 °C under vacuum. Phenol was distilled (80 °C at 20 mmHg) and kept in the dark under nitrogen. 3-Hydroxy-4-methyl-5-nitrobenzoic acid was prepared as described.[14] Final reaction mixtures were dried over anhydrous Na_2SO_4 before filtration and evaporation under reduced pressure. Column chromatography was performed with 230−400 mesh silica gel. Melting points (open-ended capillary tubes) are uncorrected. IR spectra were obtained in CH_2Cl_2, and NMR spectra were obtained in $CDCl_3$ at room temperature unless otherwise stated. NMR chemical shifts are reported in ppm (δ) downfield from internal TMS; coupling constants are given in hertz. Elemental analyses were determined by the Microanalytical Laboratories, and X-ray crystallography was carried out by the CHEXRAY Facility, College of Chemistry, University of California, Berkeley.

Methyl 3-Hydroxy-4-methyl-5-nitrobenzoate. A solution of 3-hydroxy-4-methyl-5-nitrobenzoic acid (12.0 g, 0.061 mol) and concentrated H_2SO_4 (1.5 mL) in MeOH (250 mL) was refluxed for 20 h and cooled to room temperature and the solvent was evaporated. The residue was dissolved in (3:1) $CHCl_3$−*i*PrOH (150 mL) and washed with water (3 × 100 mL). The aqueous layers were extracted with (3:1) $CHCl_3$−*i*PrOH (100 mL), and the combined organic phase was dried and evaporated. The residue was recrystallyzed from CH_2Cl_2−hexane or column chromatographed (5%Et_2O in CH_2Cl_2) to yield 12.3 g (96% yield): mp 159−160 °C; IR 1530, 1720, 3565 cm^{-1}; ^1H NMR (MeOD) δ 7.79 (d, J = 1.4, 1H), 7.55 (d, J = 1.4, 1H), 4.92 (br s, 1H), 3.91 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (MeOD) δ 166.5, 158.2, 152.1, 129.8, 126.0, 119.2, 116.4, 52.9, 12.0. Anal. Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 50.82; H, 4.33; N, 6.46.

Methyl 3-Methoxymethoxy-4-methyl-5-nitrobenzoate. To a stirred solution of methyl 3-hydroxy-4-methyl-5-nitrobenzoate (12.0 g, 57.0 mmol) in a 1:1 mixture of distilled CH_2Cl_2 (150 mL) and dimethoxymethane (150 mL) under argon was added P_2O_5 (16.2 g, 114 mmol) in small portions over a period of 1 h. The mixture was stirred overnight at room temperature, poured into an ice-cooled 10% Na_2CO_3 solution (150 mL), and extracted with ether (400 mL). The organic layer was washed with water (2 × 100 mL), dried, and evaporated, and the residue was chromatographed (CH_2Cl_2) to give 14.2 g of product as a white solid (98% yield): mp 66−67 °C; IR 1525, 1720 cm^{-1}; ^1H NMR δ 8.12 (d, J = 1.4, 1H), 7.92 (d, J = 1.4, 1H), 5.32 (s, 2H), 3.95 (s, 3H), 3.51 (s, 3H), 2.44 (s, 3H); ^{13}C NMR δ 165.0, 156.1, 150.9, 129.2, 127.6, 118.1, 117.6, 94.8, 56.4, 52.6, 12.1. Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.47; H, 5.21; N, 5.48.

Methyl 3-Amino-5-methoxymethoxy-4-methylbenzoate (8). A mixture of 10.0 g of the nitrobenzoate (0.04 mol) and 2.0 g of 10% Pd/C catalyst in 175 mL of distilled MeOH was shaken under hydrogen (60 psi) for 2 h at room temperature. The mixture was filtered through a Celite pad, which was washed thoroughly with MeOH and CH_2Cl_2, and the combined fractions were evaporated. The residue was chromatographed (3% MeOH in CH_2Cl_2) to yield 8.4 g of **8** (95%) which should be kept under argon in the fridge: mp 98−99 °C; IR 1710, 3480 cm^{-1}; ^1H NMR δ 7.16 (d, J = 1.3 Hz, 1H), 7.09 (d, J = 1.3 Hz, 1H), 5.21 (s, 2H), 3.86 (s, 3H), 3.77 (br s, 2H), 3.49 (s, 3H), 2.10 (s, 3H); ^{13}C NMR δ 167.1, 155.4, 145.6, 128.5, 116.7, 110.2, 105.3, 94.6, 56.1, 51.9, 9.5. Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.40; H, 6.71; N, 6.16.

Methyl (2*R*,3*S*)-3-[*N*-[3-[*N*-(Benzyloxycarbonyl)amino]-2-hydroxy-4-methoxy-4-oxobutyl]amino]-5-methoxymethoxy-4-methylbenzoate (12). $Mg(ClO_4)_2$ (9.0 g, 0.04 mol) was added to a stirred solution of aniline **8** (9.0 g, 0.04 mol) in freshly distilled CH_3CN (40 mL) at room temperature. When the mixture became homogeneous, a 0.33 M solution of **9** (12.7 g, 0.048 mol) in CH_3CN (145 mL) was added via cannula. The reaction mixture was stirred under argon for 46 h. The solvent was evaporated, the residue was dissolved in EtOAc (400 mL), and the solution was washed with water (200 mL) and brine (100 mL). The aqueous layers were back-extracted with EtOAc (2 × 50 mL) and the combined organic phase was dried and evaporated. The residue was chromatographed (EtOAc−hexane, 1:2) to give 17.6 g of **12** (90% yield): mp (EtOAc−hexane) 112−113 °C; IR 1720, 1750, 3420, 3600 cm^{-1}; ^1H NMR ($CDCl_3$−D_2O, main isomer) δ 7.33 (m, 5H), 7.16 (s, 1H), 7.05 (s, 1H), 5.93 (d, J = 9.1, 1H), 5.20 (s, 2H), 5.14 (s, 2H), 4.60 (br d, J = 9.1, 1H), 4.38 (br t, J = 6.1, 1H), 3.85 (s, 3H), 3.71 (s, 3H), 3.48 (s, 3H), 3.40 (dd, J = 14.0, 6.1, 1H), 3.26 (dd, J = 14.0, 7.6, 1H), 2.10 (s, 3H); ^{13}C NMR δ 171.4, 167.7, 156.9, 155.1, 146.5, 135.9, 128.44, 128.38, 128.1, 127.9, 116.6, 104.9, 104.8, 94.6, 69.4, 67.2, 56.2, 56.0, 52.6, 51.9, 45.7, 9.3. Anal. Calcd for $C_{24}H_{30}N_2O_9$: C, 58.77; H, 6.16; N, 5.71. Found: C, 59.12; H, 6.40; N, 5.89.

Methyl (2*R*,3*S*)-3-[*N*-[2-Hydroxy-4-methoxy-4-oxo-3-[*N*-(9-phenylfluoren-9-yl)amino]butyl]amino]-5-methoxymethoxy-4-methylbenzoate (13). A mixture of **12** (16.3 g, 33.3 mmol) in distilled MeOH (220 mL) and 3.25 g of 10% Pd−C was stirred under hydrogen atmosphere overnight at room temperature. The mixture was filtered through Celite and the pad was washed thoroughly with MeOH and CH_2Cl_2. The solvent was evaporated, toluene (10 mL) was added and evaporated, and the solid residue obtained was vacuum-dried, kept under nitrogen, and dissolved in anhydrous CH_3CN (60 mL). This solution was transferred via cannula to a Morton flask, and K_3PO_4 (14.1 g, 0.066 mol) and $Pb(NO_3)_2$ (11.02 g, 0.033 mol) were added, followed by a solution of PfBr (21.36 g, 0.066 mmol) in CH_3CN (50 mL). The resulting suspension was stirred under argon at room temperature for 36 h, and the supernatant was transferred via cannula to a flask. The solid residue was triturated with CH_2Cl_2 (100 mL) for 15 min and the mixture was filtered through a glass frit funnel (10−15 size pore), and the process was repeated several times. Evaporation of the solvents gave a solid that was purified through a short silica gel column (CH_2Cl_2) to eliminate the excess of PfBr. The mixture of *N*,*N*-diPf and *N*-monoPf products was suspended in 500 mL of MeOH and treated with 1 M HCl (2.5 mL). The reaction mixture was heated at reflux for 1 h, the solvent was evaporated, and the residue column was chromatographed (CH_2Cl_2 to 10% Et_2O/CH_2Cl_2) to yield the product as a white solid (16.26 g, 82% yield): mp 92−93 °C; IR 1710, 3440, 3680 cm^{-1}; ^1H NMR ($CDCl_3$−D_2O) δ 7.69 (t, J = 7.9, 2H), 7.42−7.13 (m, 12 H), 6.84 (s, 1H), 5.18 (s, 2H), 3.84 (s, 3H), 3.69 (dd, J = 11.2, 5.6, 1H), 3.47 (s, 3H), 3.31 (s, 3H), 3.14 (dd, J = 12.7, 4.5, 1H), 2.97 (dd, J = 12.7, 5.6, 1H), 2.71 (d, J = 6.7, 1H), 1.86 (s, 3H); ^{13}C NMR δ 174.6, 167.4, 154.8, 148.0, 147.8, 146.8, 143.4, 141.0, 140.1, 128.8, 128.6, 128.4, 128.2, 127.5, 127.4, 126.1, 125.8, 125.1, 120.2, 120.1, 116.6, 105.3, 105.1, 94.7, 72.5, 70.1, 57.5, 56.1, 52.0, 51.9, 45.7, 9.4. Anal. Calcd for $C_{35}H_{36}N_2O_7$: C, 70.45; H, 6.08; N, 4.69. Found: C, 70.61; H, 6.15; N, 4.77.

Preparation of Benzenesulfonic Anhydride (Bs_2O). Benzenesulfonic acid monohydrate (40 g, 0.25 mol) was suspended in benzene (100 mL) and thionyl chloride (64 mL, 0.88 mol) was added slowly. The reaction mixture was heated at reflux for 3 h, then the excess of $SOCl_2$ and benzene was distilled off under argon, the brown residual solution was

allowed to cool, dry Et_2O (30 mL) and hexane (15 mL) were added, and the solution was kept in the refrigerator overnight. The white crystals were filtered under nitrogen and dried (75% yield).

Methyl (*2S*,*3S*)-3-[*N*-[1-Benzenesulfonyl-4-methoxy-4-oxo-(2,3)-[*N*-(9-phenylfluoren-9-yl)aziridino]butyl]amino]-5-methoxymethoxy-4-methylbenzoate (14). To a solution of **13** (15.0 g, 25.1 mmol) in 120 mL of pyridine was added freshly prepared Bs_2O (18.75 g, 62.9 mmol). The reaction mixture was heated at 65 °C for 14 h, then cooled to room temperature, and the pyridine was removed under vacuum. Toluene was added and evaporated to remove traces of pyridine. The residue was washed with water (250 mL) and extracted with ether (3 × 200 mL). The combined organic phase was dried and concentrated, and the crude product was chromatographed (20 to 30% EtOAc in hexane) to give **14** as a white solid (13.73 g, 76% yield): mp 82−86 °C; $[\alpha]^{20}_D$ −14.3° (*c* 1.0, $CHCl_3$); IR 1720 cm^{-1}; ^1H NMR (2 rotamers) δ 7.70−7.05 (m, 38 H), 6.92 (d, J = 1.2, 1H), 6.76 (d, J = 1.2, 1H), 5.26−5.18 (m, 4H), 3.82 (s, 3H), 3.81 (m, 1H), 3.79 (s, 3H), 3.64 (m, 2H), 3.48 (s, 3H), 3.46 (s, 3H), 3.39 (s, 3H), 3.33 (dd, J = 14.8, 8.7, 1H), 3.19 (s, 3H), 2.20 (d, J = 6.1, 1H), 2.15 (d, J = 6.1, 1H), 2.09 (m, 1H), 2.07 (s, 3H), 1.98 (s, 3H), 1.77 (m, 1H); ^{13}C NMR (2 rotamers) δ 169.3 and 169.1, 165.9 and 165.8, 155.9, 147.0 and 146.9, 145.2 and 145.0, 142.4 and 142.3, 141.1 and 141.0, 140.2 and 139.9, 139.7 and 139.1, 138.9 and 137.9, 135.3 and 134.7, 132.9 and 132.7, 129.0 and 128.9, 128.87 and 128.85, 128.78 and 128.4, 128.2, 127.8 and 127.7, 127.62 and 127.58, 127.4, 127.2 and 127.1, 126.8 and 126.7, 126.1 and 126.0, 125.7 and 125.6, 123.7 and 123.0, 120.1, 119.9 and 119.8, 114.0 and 113.8, 94.3, 75.4, 56.2, 52.1 and 52.0, 51.8 and 51.5, 50.6 and 49.1, 39.6 and 38.9, 37.7 and 37.4, 12.3 and 11.9. Anal. Calcd for $C_{41}H_{38}N_2O_8S$: C, 68.51; H, 5.33; N, 3.90. Found: C, 68.24; H, 5.32; N, 3.97.

Methyl (3*S*,4*S*)-1-Benzenesulfonyl-7-methoxymethoxy-5-oxo-(3,4)-[*N*-(9-phenylfluoren-9-yl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[1,2-*b*]azocin-9-carboxylate (15). To a −20 °C solution of **14** (12.0 g, 16.7 mmol) in 300 mL of THF was added KHMDS (76 mL, 83.5 mmol, 1.1 M in THF). The resulting orange solution was stirred for 2 h as the temperature warmed from −20 to 3 °C, then poured over a cold mixture of 1 M KH_2PO_4 (400 mL) and ether (500 mL). After being stirred for 10 min, the organic phase was separated and washed with brine, and the aqueous phase was back extracted with Et_2O (2 × 100 mL). The combined organic phase was dried and evaporated, and the residue was dissolved in CH_2Cl_2 (∼10 mL) with stirring. EtOH (100 mL) was then added and the solution was heated at reflux for 10 min; after standing overnight, a white powder was filtered off and dried. The mother liquors were concentrated and the residue was chromatographed (CH_2Cl_2) to provide additional product. The solids from the column and the crystallization were combined to yield a total of 8.2 g of product as a white solid (72% yield): mp (CH_2Cl_2−EtOH) 220−222 °C; $[\alpha]^{20}_D$ +89.0° (*c* 1.0, $CHCl_3$); IR 1690, 1720 cm^{-1}; ^1H NMR δ 7.91 (d, J = 1.4, 1H), 7.64 (m, 5H), 7.51 (t, J = 7.7, 2H), 7.39−7.30 (m, 2H), 7.17−6.89 (m, 7H), 6.73 (d, J = 7.5, 1H), 6.62 (d, J = 7.8, 2H), 5.47 (d, J = 6.6, 1H), 5.30 (d, J = 6.6, 1H), 4.29 (dd, J = 14.3, 3.4, 1H), 3.94 (s, 3H), 3.80 (d, J = 18.1, 1H), 3.56 (s, 3H), 3.51 (d, J = 18.1, 1H), 3.50 (d, J = 14.3, 1H), 2.47 (dd, J = 6.6, 3.3, 1H), 1.96 (d, J = 6.6, 1H); ^{13}C NMR δ 204.1, 165.8, 154.3, 147.7, 142.6, 142.2, 142.1, 140.5, 139.2, 138.1, 136.4, 133.3, 129.4, 129.3, 129.0, 128.7, 128.0, 127.9, 127.8, 127.2, 127.0, 126.4, 126.3, 124.9, 121.5, 120.3, 120.1, 115.3, 95.1, 75.4, 56.6, 52.4, 48.0, 45.3, 42.5, 42.4. Anal. Calcd for $C_{40}H_{34}N_2O_7S$: C, 69.96; H, 4.99; N, 4.08. Found: C, 69.61; H, 5.22; N, 4.06.

(3*S*,4*S*)-1-Benzenesulfonyl-5-hydroxy-7-methoxymethoxy-(3,4)-[*N*-(9-phenylfluoren-9-yl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[1,2-*b*]azocin-9-methanol (31). Ketone **15** (5.5 g, 8.0 mmol) in 50 mL of THF was added to a suspension of $LiAlH_4$ (910 mg, 24.0 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred for 20 min, EtOAc (15 mL) was added, followed by sat. Na_2CO_3 (5 mL), $CHCl_3$ (150 mL), KH_2PO_4, and Na_2SO_4. The resulting mixture was stirred at room temperature for 1 h and then filtered. The precipitate was washed with $CHCl_3$, the combined clear filtrate and washings were evaporated, and the residue was chromatographed (10% Et_2O−CH_2Cl_2) to give **31** as a white solid (5.13 g, 97% yield). **31a**: mp (EtOH) 204−207 °C dec; ^1H NMR δ 7.64−7.13 (m, 19 H), 6.96 (s, 1H), 6.89 (br s, 1H), 5.07 (m, 2H), 4.57 (d, J = 5.5, 2H), 4.48 (dd, J = 12.6, 4.3, 1H), 3.81 (br m, 1H), 3.40 (br m, 1H), 3.35 (s, 3H), 2.90 (d, J = 4.3, 1H, OH), 2.63 (br s, 1H), 2.05 (br s, 1H), 1.78 (br s, 1H, OH), 1.24 (br s, 1H); ^{13}C NMR δ 154.7, 147.9, 144.8, 142.7, 141.3, 140.4, 139.5, 138.2, 132.8, 128.9, 128.8, 128.7, 128.3, 128.0, 127.5, 127.2, 127.1, 126.4, 126.1, 125.0, 122.7, 120.0, 119.9, 111.7, 94.2, 75.1, 64.2, 63.7, 56.0, 53.3, 51.7, 38.6, 30.2. Anal. Calcd for $C_{39}H_{36}N_2O_6S$: C, 70.89; H, 5.49; N, 4.24. Found: C, 70.56; H, 5.52; N, 4.14. **31b**: mp (CH_2Cl_2−EtOH) 202−204 °C dec; ^1H NMR δ 7.5−6.98 (m, 20 H), 6.22 (br s, 1H), 5.09 (br s, 2H), 4.66 (br s, 1H), 4.44 (br s, 2H), 4.19 (br m, 1H), 3.65 (br m, 1H), 3.38 (s, 3H), 2.80 (br m, 1H), 2.73 (br m, 1H), 1.24 (br s, 2H), 1.16 (br s, 1H); ^{13}C NMR δ 155.7, 148.5, 145.7, 143.3, 141.2, 140.3, 140.1, 138.8, 138.2, 132.8, 129.3, 128.9, 128.8, 128.3, 127.9, 127.4, 127.2, 126.8, 126.0, 125.4, 120.3, 120.1, 112.8, 94.7, 75.5, 70.9, 64.3, 56.2, 52.1, 43.2, 34.9, 30.6. Anal. Calcd for $C_{39}H_{36}N_2O_6S$: C, 70.89; H, 5.49; N, 4.24. Found: C, 71.09; H, 5.45; N, 4.20.

(3*S*,4*S*)-1-Benzenesulfonyl-7-methoxymethoxy-5-oxo-(3,4)-[*N*-(9-phenylfluoren-9-yl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[*b*]azocine-9-carbaldehyde (16). DMSO (2.4 mL, 33.8 mmol) was added to a solution of $(COCl)_2$ (1.4 mL, 16.0 mmol) in CH_2Cl_2 (75 mL) at −78 °C. After 15 min, diol **31** (5.0 g, 7.57 mmol) in 75 mL of CH_2Cl_2 was added and the mixture was stirred for 3 h at −78 °C. Triethylamine (10.5 mL, 75.7 mmol) was added slowly and the mixture was stirred for 10 min at −78 °C and then warmed to room temperature. Ice water (100 mL) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with brine, dried, and evaporated to give a residue that was chromatographed (30% EtOAc−hexane) to yield 4.67 g of **16** (94%): mp 137−140 °C; $[\alpha]^{20}_D$ +87.9° (*c* 1.0, $CHCl_3$); IR 1685 cm^{-1}; ^1H NMR δ 9.90 (s, 1H), 7.79−7.49 (m, 8H), 7.38−7.05 (m, 5H), 6.95−6.83 (m, 4H), 6.72 (d, J = 7.5, 1H), 6.61 (d, J = 7.3, 2H), 5.49 (d, J = 6.7, 1H), 5.33 (d, J = 6.7, 1H), 4.32 (dd, J = 14.3, 3.3, 1H), 3.83 (d, J = 18.3, 1H), 3.57 (s, 3H), 3.55 (d, J = 18.3, 1H), 3.53 (d, J = 14.3, 1H), 2.48 (dd, J = 6.6, 3.3, 1H), 1.99 (d, J = 6.6, 1H); ^{13}C NMR δ 203.7, 190.2, 155.1, 147.6, 142.6, 142.1, 142.0, 141.3, 139.2, 138.2, 138.0, 135.9, 133.5, 129.3, 129.1, 128.0, 127.7, 127.2, 127.1, 126.4, 126.3, 124.8, 121.2, 120.3, 120.2, 115.1, 95.2, 75.5, 56.7, 48.1, 45.4, 42.7, 42.4. Anal. Calcd for $C_{39}H_{32}N_2O_6S$: C, 71.33; H, 4.91; N, 4.27. Found: C, 71.16; H, 4.98; N, 4.38.

(3*S*,4*S*)-1-Benzenesulfonyl-9-diethoxymethyl-7-methoxymethoxy-(3,4)-[*N*-(9-phenylfluoren-9-yl)aziridino]-2,3,4,6-tetrahydro-1*H*-benzo[1,2-*b*]azocin-5-one (17). To a solution of aldehyde **16** (4.5 g, 6.86 mmol) in a 1:2 mixture of EtOH:THF (30 mL) was added *p*-TsOH (325 mg, 1.71 mmol) and triethyl orthoformate (10 mL), and the resulting solution was stirred for 5 h at room temperature. The solvents were evaporated, the residue was dissolved in CH_2Cl_2 (200 mL), and the solution was washed with aq $NaHCO_3$ (100 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), the combined organic phase was washed with H_2O (2 × 75 mL), dried, and evaporated, and the residue was chromatographed (5% Et_2O−CH_2Cl_2) to yield 4.66 g (93%) of the acetal **17**: mp (CH_2Cl_2−EtOH) 142−144 °C; $[\alpha]^{20}_D$ +80.0° (*c* 0.6, $CHCl_3$); IR 1690 cm^{-1}; ^1H NMR δ 7.67−7.29 (m, 10H), 7.19−6.96 (m, 6H), 6.78 (d, J = 7.5, 1H), 6.70 (d, J = 7.2, 2H), 6.43 (s, 1H), 5.43 (s, 1H), 5.40 (d, J = 6.5, 1H), 5.26 (d, J = 6.5, 1H), 4.31 (dd, J = 14.3, 3.5, 1H), 3.78 (d, J = 17.7, 1H), 3.55 (s, 3H), 3.62−3.47 (m, 6H), 2.49 (dd, J = 6.6, 3.4, 1H), 1.97 (d, J = 6.6, 1H), 1.25 (t, J = 7.0, 3H), 1.24 (t, J = 7.0, 3H); ^{13}C NMR δ 205.0,

154.3, 147.8, 142.8, 142.3, 142.1, 139.7, 139.2, 139.1, 138.7, 132.9, 130.7, 129.1, 128.8, 128.6, 128.0, 127.9, 127.8, 127.0, 126.9, 126.5, 126.3, 125.1, 120.2, 120.0, 118.2, 113.0, 100.7, 95.1, 75.5, 61.2, 61.1, 56.4, 48.2, 45.3, 42.5, 42.4, 15.2 (2C). Anal. Calcd for $C_{43}H_{42}N_2O_7S$: C, 70.67; H, 5.79; N, 3.83. Found: C, 70.32; H, 5.87; N, 3.80.

(3*S*,4*S*)-1-Benzenesulfonyl-9-diethoxymethyl-7-methoxymethoxy-6-methylene-(3,4)-[*N*-(9-phenylfluoren-9-yl)-aziridino]-2,3,4,6-tetrahydro-1*H*-benzo[1,2-*b*]azocin-5-one (21). Paraformaldehyde (185 mg, 6.16 mmol) was suspended in DMSO (20 mL) and Triton B (1M solution in DMSO−MeOH, 820 μL, 0.82 mmol) was added; a homogeneous solution was obtained after stirring at room temperature for a couple of minutes. A solution of **17** (3.0 g, 4.1 mmol) in DMSO (10 mL) was added, and the mixture was heated at 65 °C for 1.5 h. After cooling to room temperature, water was added, and the mixture was extracted with EtOAc (2 × 100 mL). The combined organic phase was washed with brine (50 mL), dried, and evaporated to a white residue that was purified by column chromatography (5% $Et_2O-CH_2Cl_2$) to give **21** as a white solid (2.96 g, 97% yield): mp 107−110 °C; $[\alpha]^{20}_D$ +11.6° (*c* 1.0, $CHCl_3$); IR 1680 cm^{-1}; ^1H NMR δ 7.63−7.07 (m, 15 H), 6.85 (m, 3H), 6.51 (br m, 2H), 6.37 (br s, 1H), 6.13 (br s, 1H), 5.32−5.26 (m, 3H), 4.07 (br d, J = 12.4, 1H), 3.57 (br m, 7H), 3.29 (br d, J = 13.7, 1H), 2.43 (d, J = 6.4, 1H), 2.03 (br s, 1H), 1.24 (br m, 6H); ^{13}C NMR δ 197.2, 154.8, 145.9, 145.5, 142.3, 140.6, 140.4, 140.3, 139.8, 137.9, 132.9, 129.7, 128.7, 128.6, 128.1, 127.9, 127.4, 126.8, 126.6, 125.8, 119.8, 117.9, 113.3, 100.5, 95.0, 75.5, 61.1 (2C), 56.5, 48.0, 44.4, 44.1, 15.15, 15.12. Anal. Calcd for $C_{44}H_{42}N_2O_7S$: C, 71.14; H, 5.70; N, 3.77. Found: C, 70.79; H, 5.66; N, 3.66.

Preparation of Epoxy Ketone 22. To a stirred solution of enone **21** (1.7 g, 2.3 mmol) in THF (30 mL) was added 70% *t*-BuOOH (350 μL, 2.5 mmol) followed by Triton B (40% in MeOH, 160 μL, 0.35 mmol). The resulting solution was stirred for 20 min at room temperature, then partitioned between water and EtOAc. The organic phase was dried and evaporated, and the residue was chromatographed (2:3 EtOAc−hexane) to give 1.34 g of the main epoxide **22a** (77% yield): mp ($Et_2O-CH_2Cl_2$−hexane) 118−121 °C; $[\alpha]^{20}_D$ +83.3° (*c* 1.0, $CHCl_3$); IR 1700 cm^{-1}; ^1H NMR δ 7.75 (d, J = 7.4, 2H), 7.66−7.59 (m, 3H), 7.49 (m, 2H), 7.34 (m, 3H), 7.15−6.97 (m, 6H), 6.76 (m, 3H), 6.63 (s, 1H), 5.44 (s, 1H), 5.23 (m, 2H), 4.32 (br d, J = 4.9, 1H), 4.15 (br d, J = 13.7, 1H), 3.61−3.45 (m, 8H), 2.57 (br d, J = 4.8, 1H), 2.42 (br s, 1H), 2.12 (br d, J = 5.6, 1H), 1.24 (br s, 6H); ^{13}C NMR δ 199.6, 156.1, 147.3, 143.8, 143.4, 142.1, 141.9, 141.6, 139.4, 137.7, 133.2, 129.1, 128.9, 128.7, 128.6, 128.0, 127.6, 127.1, 127.0, 126.5, 126.2, 125.3, 120.2, 120.0, 118.8, 114.4, 100.2, 95.4, 75.4, 61.2, 61.1, 59.3, 56.7, 55.3, 48.8, 45.4, 41.4, 15.1, 15.1. Anal. Calcd for $C_{44}H_{42}N_2O_8S$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.45; H, 5.87; N, 3.71. Minor epoxide **22b** (17%): white crystals, mp 117−119 °C (CH_2Cl_2−hexane); $[\alpha]^{20}_D$ +28.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 55 °C) δ 7.68 (d, J = 7.6, 2H), 7.60−7.07 (m, 15H), 6.96 (d, J = 7.5, 1H), 6.85 (br s, 1H), 6.74 (br s, 1H), 5.37 (s, 1H), 5.15 (d, J = 6.5, 1H), 5.09 (d, J = 6.5, 1H), 4.01 (br d, J = 10.4, 1H), 3.50 (m, 6H), 3.43 (s, 3H), 3.26 (m, 2H), 2.44 (d, J = 6.4, 1H), 1.18 (q, J = 7.0, 6H, 1H); ^{13}C NMR ($CDCl_3$, 55 °C) δ 198.0, 156.1, 147.0, 145.1, 142.4, 141.5, 141.3, 140.8, 140.3, 138.1, 133.0, 128.8, 128.7, 128.4, 128.0, 127.6, 127.4, 126.9, 126.8, 126.4, 125.7, 119.83, 119.81, 114.7, 100.4, 95.7, 75.6, 61.2, 61.16, 58.4, 56.3, 54.1, 49.1, 44.7, 15.1. Anal. Calcd for $C_{44}H_{42}N_2O_8S$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.30; H, 5.71; N, 3.72.

Recycling of 22b (minor product in the epoxidation of the enone 21 with TBHP and Triton B in THF). A solution of epoxide **22b** (2.2 g, 2.9 mmol) in a 2:1 mixture of THF:MeOH at −78 °C was treated with a 0.1 M solution of SmI_2 in THF (Aldrich, 58 mL, 5.8 mmol). The resulting solution was stirred for 10 min at −78 °C; excess reagent was quenched by addition of pH 8.0 phosphate buffer (100 mL), and the mixture was warmed to room temperature. The aqueous phase was extracted four times with Et_2O and the combined organic layer was dried and evaporated. The residue was purified by column chromatography (EtOAc:hexane, 2:3) to yield 1.77 g of enone **21** (82% yield). A very little amount of β-hydroxy ketone was isolated (12%).

(3*S*,4*S*)-1-Benzenesulfonyl-9-diethoxymethyl-6-hydroxymethyl-7-methoxymethoxy-(3,4)-[*N*-(9-phenylfluoren-9-yl)aziridino]-2,3,4,6-tetrahydro-1*H*-benzo[*b*]azocin-5-one (23). A suspension of **22** (1.0 g, 1.32 mmol) and 10% Pd−C (200 mg) in anhydrous methanol (60 mL) and pyridine (55 μL, 0.68 mmol) was stirred under hydrogen for 3.5 d at 60 psi. The catalyst was removed by filtration and washed thoroughly with methanol, and the combined filtrate and washings were evaporated. The residue was chromatographed (EtOAc−hexane, 2:3) to give **23** as a white foam (905 mg, 90% yield): mp (EtOAc−hexane) 172−175 °C (softens) 203−206 °C dec; $[\alpha]^{20}_D$ +59.8° (*c* 1.0, $CHCl_3$); IR 1680 cm^{-1}; ^1H NMR δ 7.74−7.31 (m, 10H), 7.20−6.94 (m, 6H), 6.78 (d, J = 7.5, 1H), 6.66 (m, 2H), 6.40 (d, J = 1.0, 1H), 5.52 (d, J = 6.6, 1H), 5.43 (s, 1H), 5.34 (d, J = 6.6, 1H), 4.50 (m, 1H), 4.23 (dd, J = 14.1, 3.7, 1H), 3.89 (dd, J = 8.9, 3.0, 1H), 3.69−3.51 (m, 5H), 3.57 (s, 3H), 3.42 (d, J = 14.1, 1H), 2.97 (dd, J = 11.0, 3.6, 1H), 2.51 (dd, J = 6.7, 3.6, 1H), 2.00 (d, J = 6.7, 1H), 1.25 (t, J = 7.0, 6H); ^{13}C NMR δ 207.8, 154.8, 147.6, 142.7, 142.3, 142.2, 140.2, 139.9, 139.0, 138.3, 133.3, 130.6, 129.2, 129.1, 128.9, 128.4, 128.1, 127.9, 127.1, 126.9, 126.5, 126.4, 125.1, 120.3, 120.1, 117.7, 112.8, 100.7, 94.7, 75.5, 62.4, 61.34, 61.30, 56.6, 53.2, 48.7, 44.7, 42.6, 15.24, 15.21. Anal. Calcd for $C_{44}H_{44}N_2O_8S$: C, 69.46; H, 5.83; N, 3.68. Found: C, 69.11; H, 5.93; N, 3.67.

(3*S*,4*S*)-1-Benzenesulfonyl-6-carbamoyloxymethyl-9-diethoxymethyl-7-methoxymethoxy-(3,4)-[*N*-(9-phenylfluoren-9-yl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[*b*]azocin-5-ol (24). A solution of hydroxyketone **23** (500 mg, 0.66 mmol) in THF (5 mL) was cooled at 0 °C and treated with trichloroacetyl isocyanate (90 μL, 0.75 mmol). The cooling bath was removed and the solution stirred for 20 min. EtOH was then added (0.5 mL), the solvents were evaporated, and the residue was dissolved in EtOH (25 mL), cooled to 0 °C, and treated with $NaBH_4$ (380 mg, 9.9 mmol). The cooling bath was removed and the reaction mixture was stirred at room temperature for 22 h. The solution was poured into a 3:1 mixture of CH_2Cl_2−pH 7 phosphate buffer (200 mL), the aqueous layer was neutralized with 1 M KH_2PO_4, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layer was washed with brine (50 mL), dried, and evaporated. The residue was chromatographed (60% EtOAc−hexane + 1% Et_3N) to yield the product as a white foam (423 mg, 80% yield): mp 118−120 °C; IR 1720, 3420, 3525 cm^{-1}. ^1H NMR (∼2:1 mixture of epimers) δ 7.88−6.98 (m, 40H), 5.28 (s, 1H), 5.27 (s, 1H), 5.12 (s, 2H), 5.03 (d, J = 6.9, 1H), 5.01 (d, J = 6.9, 1H), 4.88 (br t, J = 10.5, 2H), 4.68 (m, 4H), 4.58−4.26 (m, 3H), 4.19−4.01 (m, 2H), 3.81 (m, 1H), 3.59−3.14 (m, 16H), 2. 90 (m, 1H), 2.68 (m, 1H), 2.49 (m, 1H), 2.35 (m, 1H), 1.81 (br s, 1H), 1.76 (m, 1H), 1.49 (m, 2H), 1.18 (m, 12H). Anal. Calcd for $C_{45}H_{47}N_3O_9S$: C, 67.06; H, 5.88; N, 5.21 Found: C, 67.02; H, 6.08; N, 5.03.

(3*S*,4*S*)-6-Carbamoyloxymethyl-9-diethoxymethyl-7-methoxymethoxy-(3,4)-[*N*-(9-phenylfluoren-9-yl)aziridino]-1,2,3,4,5,6-hexahydrobenzo[*b*]azocin-5-ol (25). A standard electrochemical H-cell was assembled using an extra course frit and rubber seals. The cell was equipped with a platinum-foil anode, mercury-pool cathode, silver wire reference electrode, and nitrogen bubbler. Both chambers were charged with a total 100 mL of a 0.1−0.2 M TEAB solution and, in addition, solid TEAB was added to the anode chamber to form a saturated solution. The cathode solution was deoxygenated with nitrogen for 10 min. Pre-electrolysis at −1.6 V was performed for 5−10 min to achieve a background current of 0.2 mA. Current to the cell was shut off, phenol (142 mg, 1.5 mmol) was added and, after degassing for 5 min, pre-electrolyzed again at −1.6 V to a background current of

0.5 mA. Current was again turned off and compound **24** (405 mg, 0.5 mmol) was added. After degassing for 5 min, electrolysis was conducted at −1.5 V for 8 h, when no more starting material was detected by TLC and with the background current measuring 1.1 mA. The contents of both chambers were simultaneously poured into two 250-mL Erlenmeyer flasks positioned side-by-side. The cathode solution was decanted from the Hg which was then washed with reagent grade acetonitrile (25 mL). The combined solution was partitioned between a 4:1 mixture of CH_2Cl_2:H_2O (300 mL), and the organic layer was washed with water (2 × 50 mL), dried, and evaporated. Column chromatography (3% MeOH−CH_2Cl_2) of the residue afforded the product as a white solid (305 mg, 91% yield): mp 113−116 °C; ^{1}H NMR (∼2:1 mixture of epimers) δ 7.64 (m, 4H), 7.39−7.12 (m, 21H), 7.04 (d, J = 7.4, 1H), 6.69 (s, 1H), 6.56 (s, 1H), 6.41 (s, 1H), 6.34 (s, 1H), 5.28 (s, 1H), 5.26 (s, 1H), 5.17 (t, J = 6.6, 2H), 5.06 (d, J = 6.6, 1H), 5.03 (d, J = 6.6, 1H), 4.75−4.53 (m, 8H), 4.34 (dd, J = 10.5, 4.9, 1H), 4.03 (m, 1H), 3.71 (m, 6H), 3.61−3.40 (m, 10H), 3.47 (s, 3H), 3.36 (s, 3H), 3.25 (m, 1H), 3.09 (m, 1H), 1.81 (m, 3H), 1.48 (t, J = 6.6, 1H), 1.19 (t, J = 7.0, 6H), 1.18 (t, J = 6.9, 6H); ^{13}C NMR δ 157.1, 157.0, 156.4, 156.1, 149.0, 148.8, 147.9, 145.4, 143.8, 143.1, 141.5, 140.7, 140.5, 139.5, 138.9, 138.5, 128.8, 128.6, 128.4, 128.3, 128.3, 128.1, 127.6, 127.4, 127.1, 127.0, 126.8, 126.6, 126.5, 126.4, 126.1, 125.6, 125.2, 120.0, 119.9, 119.8, 119.6, 115.2, 111.5, 104.3, 101.3, 101.1, 94.9, 94.1, 75.6, 74.9, 73.3, 67.4, 64.3, 61.2, 61.1, 56.6, 56.1, 49.7, 48.7, 44.6, 41.6, 39.1, 39.0, 15.1 (4C). Anal. Calcd for $C_{39}H_{43}N_3O_7$: C, 70.36; H, 6.51; N, 6.31. Found: C, 70.26; H, 6.71; N, 5.94.

(3*S*,4*S*)-6-Carbamoyloxymethyl-9-diethoxymethyl-5-hydroxy-7-methoxymethoxy-(3,4)-[*N*-(9-phenylfluoren-9-yl)aziridino]-3,4,5,6-tetrahydro-2*H*-benzo[*b*]azocin-1-yl Acetate (26). Compound **25** (70 mg, 0.1 mmol) was dissolved in THF (2 mL), Davis' oxaziridine (35 mg, 0.13 mmol) was added at once, and the resulting solution was stirred at room temperature under nitrogen. More aziridine was added twice at intervals of 1 h (2 × 27 mg). After a total reaction time of 3 h, the solvent was removed, the residue was chromatographed, and 45 mg of hydroxylamine were collected (63% yield). This material was dissolved in Ac_2O (0.5 mL) and NaOAc (10 mg, 0.12 mml) was added. The mixture was stirred at room temperature for 1 h, then CH_2Cl_2 (10 mL) and EtOH (0.5 mL) were added. The solution was stirred for 5 min, then washed with sat $NaHCO_3$ (2 × 10 mL), H_2O (10 mL), and brine, dried, and concentrated. The residue was chromatographed (2:1 EtOAc:hexane to EtOAc) to yield 48 mg of **26** (92%): mp 111−114 °C; ^{1}H NMR δ 7.66 (d, J = 7.6, 1H), 7.63 (d, J = 7.6, 1H), 7.39−7.26 (m, 4H), 7.20−7.02 (m, 6H), 6.74 (br m, 3H), 5.61 (br s, 1H), 5.56 (s, 1H), 5.37 (d, J = 6.4, 1H), 5.27 (d, J = 6.5, 1H), 4.68 (br s, 2H), 4.30−4.22 (m, 3H), 3.74−3.56 (m, 7H), 3.52 (s, 3H), 2.03 (s, 3H), 1.86 (br s, 1H), 1.81 (t, J = 7.0, 1H), 1.32 (t, J = 7.0, 6H); ^{13}C NMR δ 168.8, 157.0, 154.8, 149.6, 148.2, 144.7, 143.1, 141.8, 139.5, 128.7, 128.4, 127.9, 127.6, 126.9, 126.8, 126.3, 125.5, 119.9, 119.7, 113.0, 111.1, 101.5, 95.1, 75.9, 67.3, 64.7, 61.6, 61.5, 58.8, 56.4, 40.0, 39.4, 35.8, 19.2, 15.2 (2C). Anal. Calcd for $C_{41}H_{45}N_3O_9$: C, 68.03; H, 6.27; N, 5.81. Found: C, 67.92; H, 6.40; N, 5.62.

(3*S*,4*S*)-6-Carbamoyloxymethyl-9-diethoxymethyl-7-methoxymethoxy-5-oxo-(3,4)-[*N*-(9-phenylfluoren-9-yl)-aziridino]-3,4,5,6-tetrahydro-2*H*-benzo[*b*]azocin-1-yl Acetate (27). A solution of alcohol **26** (73 mg, 0.1 mmol) in 2 mL of CH_2Cl_2 was added to a stirred solution of DMP (64 mg, 0.15 mmol) in CH_2Cl_2 (5 mL), and the resulting solution was stirred at room temperature for 20 min. Et_2O (10 mL) was added and the mixture was poured into 20 mL of sat aq $NaHCO_3$ containing 2.5 g of $Na_2S_2O_3$. The mixture was stirred for 5 min, more Et_2O (25 mL) was added, and the organic layer was washed with sat $NaHCO_3$ (10 mL) and H_2O (10 mL), dried, and concentrated. Column chromatography of the residue (3:2 EtOAc:hexane) afforded 67 mg of product (91% yield): mp 114−117 °C; $[\alpha]^{20}_D$ +102.4° (*c* 0.9, $CHCl_3$); ^{1}H NMR δ 7.68 (d, J = 7.5, 1H), 7.61 (d, J = 7.5, 1H), 7.38 (m, 3H), 7.31 (t, J = 7.5, 1H), 7.20−7.04 (m, 6H), 6.83 (d, J = 7.5, 1H), 6.67 (d, J = 7.0, 2H), 5.60 (s, 1H), 5.45 (d, J = 6.5, 1H), 5.32 (d, J = 6.5, 1H), 4.67 (dd, J = 10.7, 7.2, 1H), 4.47 (br s, 2H), 4.27 (dd, J = 10.7, 2.9, 1H), 3.81−3.63 (m, 6H), 3.57 (m, 1H), 3.56 (s, 3H), 2.50 (dd, J = 6.7, 4.3, 1H), 1.94 (d, J = 6.7, 1H), 1.93 (s, 3H), 1.34 (t, J = 7.0, 6H); ^{13}C NMR δ 201.3, 167.4, 156.8, 153.9, 150.0, 148.2, 142.5, 142.4, 142.3, 140.6, 138.9, 129.1, 128.6, 128.0, 127.8, 126.9, 126.8, 126.5, 125.2, 124.9, 120.2, 119.9, 113.9, 111.8, 101.3, 95.1, 75.4, 63.3, 61.6, 61.5, 56.5, 56.4, 48.4, 41.9, 41.6, 19.3, 15.2 (2C). Anal. Calcd for $C_{41}H_{43}N_3O_9$: C, 68.22; H, 6.00; N, 5.82. Found: C, 68.10; H, 6.11; N, 5.87.

Preparation of 28. A solution of **27** (60 mg, 0.08 mmol) in a 1:1 mixture of CH_2Cl_2:MeOH (3 mL) was cooled to 0 °C, hydrazine monohydrate was added (2 drops), and the solution was stirred for 30 min, The solvent was evaporated, the residue was dissolved in CH_2Cl_2 (10 mL), and the solution was washed with water (4 × 5 mL), dried, and concentrated, and the residue was chromatographed (40% EtOAc:hexane) to afford the product in 97% yield (55 mg): mp 110−112 °C; $[\alpha]^{20}_D$ +90.5° (*c* 1.4, $CHCl_3$); ^{1}H NMR δ 7.68 (d, J = 7.5, 1H), 7.62 (d, J = 7.5, 1H), 7.37 (t, J = 7.5, 1H), 7.31 (t, J = 7.5, 1H), 7.17−7.01 (m, 6H), 6.90 (d, J = 7.5, 1H), 6.85 (d, J = 7.5, 1H), 6.77 (m, 3H), 6.36 (br s, 1H), 5.56 (s, 1H), 5.50 (d, J = 6.3, 1H), 5.27 (d, J = 6.3, 1H), 4.79 (dd, J = 12.2, 1.0, 1H), 4.69 (br s, 2H), 4.41 (dd, J = 12.4, 4.4, 1H), 3.82−3.63 (m, 6H), 3.54 (s, 3H), 2.61 (d, J = 3.4, 1H), 2.13 (dd, J = 6.7, 1.8, 1H), 1.71 (d, J = 6.7, 1H), 1.33 (t, J = 7.0, 3H), 1.32 (t, J = 7.0, 3H); ^{13}C NMR δ 158.5, 154.3, 150.7, 149.0, 143.1, 142.5, 139.2, 138.9, 129.0, 128.3, 128.0, 127.6, 126.9, 126.8, 126.5, 125.2, 120.2, 119.9, 115.5, 110.2, 105.7, 101.7, 94.3, 93.2, 75.4, 61.7, 61.4, 56.5, 53.2, 41.2, 39.0, 30.3, 15.3. Anal. Calcd for $C_{39}H_{41}N_3O_8$: C, 68.91; H, 6.08; N, 6.18. Found: C, 68.78; H, 6.16; N, 6.12.

Preparation of 29. A solution of **28** (35 mg, 0.05 mmol) and acetic anhydride (140 μL, 1.5 mmol) in pyridine (0.5 mL) containing DMAP (6 mg, 0.05 mmol) was stirred at room temperature for 12 h. Et_2O was added (5 mL) and the organic phase was washed with 1% HCl (3 mL), sat $NaHCO_3$ (5 mL), and brine (5 mL), dried, and concentrated, and the residue was chromatographed (2:1, EtOAc:hexane) to yield the product as a white foam in 88% yield (33 mg): $[\alpha]^{20}_D$ +116.0° (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.69 (d, J = 7.7, 1H), 7.67 (d, J = 7.7, 1H), 7.36 (dd, J = 7.2, 13.6, 2H), 7.20−6.76 (m, 11H), 5.56 (s, 1H), 5.45 (d, J = 6.3, 1H), 5.27 (d, J = 6.3, 1H), 4.59 (br s, 2H), 4.28 (m, 2H), 3.85−3.62 (m, 6H), 3.59 (s, 3H), 3.39 (d, J = 5.8, 1H), 2.11 (d, J = 6.6, 1H), 2.02 (d, J = 6.6, 1H), 1.99 (s, 3H), 1.31 (t, J = 6.9, 3H), 1.30 (t, J = 6.9, 3H); ^{13}C NMR δ 168.0, 156.4, 154.4, 149.7, 148.1, 143.6, 143.0, 142.3, 139.6, 139.2, 128.9, 128.4, 128.0, 127.8, 126.9, 126.8, 126.7, 126.3, 125.5, 120.1, 119.7, 114.6, 109.6, 106.0, 101.4, 98.8, 94.4, 75.4, 63.4, 61.4, 61.2, 56.5, 53.1, 38.9, 37.8, 29.2, 21.7, 15.3, 15.2. Anal. Calcd for $C_{41}H_{43}N_3O_9$: C, 68.22; H, 6.00; N, 5.82. Found: C, 68.13; H, 6.14; N, 5.73.

Preparation of FK973. Compound **28** (10 mg, 0,014 mmol) was cooled at 0 °C under an argon atmosphere and treated with a cooled solution of Et_3SiH in TFA (105 mol %, 1 mL from a previously prepared solution of 25 μL of Et_3SiH in 5 mL of TFA). The resulting mixture, which became heterogeneous in 15 min, was stirred at 0−5 °C for 20 h. Ice water (3 mL) and CH_2Cl_2 (5 mL) were added, the aqueous layer was extracted with CH_2Cl_2 (3 mL), and the combined organic phase was dried, filtered, and evaporated to give phenylfluorene. The aqueous phase was evaporated and dried under vacuum, and the crude product was dissolved in pyridine (0.5 mL) and treated with Ac_2O (60 μL). The resulting solution was stirred at room temperature for 18 h. The solvent was removed under vacuum, and toluene was added and evaporated to remove traces of pyridine. The residue was partitioned between CH_2Cl_2 (5 mL) and water (5 mL), the aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL), and the combined organic phase was dried and concentrated. The crude product was chromatographed (EtOAc) to give FK973 (52% yield).

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