# Synthesis of Fluorinated Macrocyclic Bis(indolyl)maleimides as Potential $^{19}$F NMR Probes for Protein Kinase C

Peter G. Goekjian,* Guo-Zhang Wu,† Shi Chen, and Lanxin Zhou

*Department of Chemistry, Mississippi State University, Mississippi State, Mississippi 39762*

Michael R. Jirousek† and James R. Gillig

*Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Indiana 46285*

Lawrence M. Ballas† and Jeffrey T. Dixon

*Sphinx Pharmaceutical Corporation, Durham, North Carolina 27712*

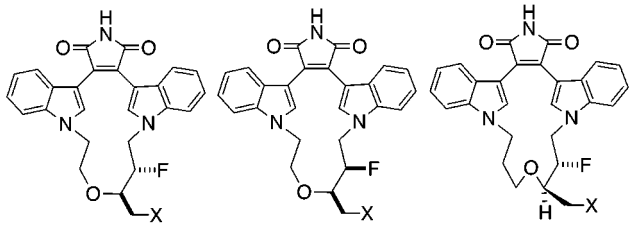
*Received May 8, 1998*

Six macrocyclic bis(indolyl)maleimides **1**−**6** bearing a fluorine label on the aliphatic portion of the macrocycle have been prepared as potential fluorine NMR probes for the catalytic domain of protein kinase C. The macrocyclic bis(indolyl)maleimides such as LY333531 are reversible, ATP competitive, and isoform-selective inhibitors of protein kinase C and may thus serve to probe for subtle differences between protein kinase catalytic domains. The key stereochemical elements were put in place by a Welch aldol condensation between ethyl fluoroacetate and (*R*)-cyclohexylidene glyceraldehyde, which was followed by allylation of the secondary alcohol, elaboration of the alkene and ester to alcohols, and mesylation. The macrocycle was formed by slow addition of a mixture of the fluorine-labeled aliphatic dimesylate and *N*-methyl 2,3-bis[1*H*-indol-3-yl]maleimide to a suspension of cesium carbonate. Adjusting the functionality led to the six fluorine-labeled macrocyclic bis(indolyl)-maleimides. These compounds retain the high potency of the parent compounds, with $IC_{50}$ values below 5 nM for the 14-membered ring compounds **1**−**3** and 13−90 nM for the 15-membered ring compounds **5**−**6**. Vicinal proton−fluorine coupling constants provide an experimental parameter for determining the local macrocycle conformation.

## Introduction

The macrocyclic bis(indolyl)maleimides, e.g., LY333531, are a class of isoform-selective protein kinase C (PKC) inhibitors recently developed at Eli Lilly and Co. that show excellent selectivity for individual isoforms of PKC, as well as for PKC over other protein kinases.[1] The fact that these inhibitors are ATP-competitive and that the bis(indolyl)maleimides have been shown to inhibit the proteolytically activated catalytic domain,[2] PKM, suggests that although the catalytic domains of protein kinases are highly conserved,[3] sufficient differences exist even among the most closely related to allow for selective inhibition.[4]

Signal transduction has evolved as an important target for pharmacological intervention, offering a general approach to manipulating the endocrine regulatory system.[5] The problem of controlling signal transduction can be reduced to the issue of selectively inhibiting protein kinases and protein phosphatases, and the selective inhibition of protein kinases has therefore attracted considerable interest in recent years.[6] Protein kinase C in particular has been invoked as a potential target in the treatment of an impressive array of disease states




* Please address correspondence to this author at Tel: (601) 325-7614; FAX: (601) 325-1618; E-mail: pgg1@ra.msstate.edu.

† Present addresses: G.-Z. Wu, Tyger Scientific, Inc. Princeton, NJ 08543-2358. M. R. Jirousek, Abbott Laboratories, Abbott Park, IL 60064. L. M. Ballas, Novalon Pharmaceutical Corp., Durham, NC 27703-8466.

(1) Ishii, H.; Jirousek, M. R.; Koya, D.; Takagi, C.; Xia, P.; Clermont, A.; Bursell, S.-E.; Kern, T. S.; Ballas, L. M.; Heath, W. F.; Stramm, L. E.; Feener, E. P.; King, G. L. *Science* **1996**, *272*, 728.

(2) Wilkinson, S. E.; Parker, P. J.; Nixon, J. S. *Biochem. J.* **1993**, *294*, 335.

(3) *The Protein Kinase Facts Book*; Hardie, G., Hanks, S., Eds.; Academic Press: San Diego, 1995.

(4) For recent crystal structures of ATP-competitive inhibitors bound to the protein kinase ATP-binding site, please see: (a) Lawrie, A.; Noble, M.; Tunnah, P.; Brown, N.; Johnson, L.; Endicott, J. *Nat. Struct. Biol.* **1997**, *4*, 796. (b) Prade, L.; Engh, R.; Girod, A.; Kinzel, V.; Huber, R.; Bossemeyer, D. *Structure* **1997**, *5*, 1627. (c) Wilson, K.; McCaffrey, P.; Hsiao, K.; Pazhanisamy, S.; Galullo, V.; Bemis, G.; Fitzgibbon, M.; Garon, P.; Murcko, M.; Su, M. *Chem. Biol.* **1997**, *4*, 423. (d) Tong, L.; Pav, S.; White, D.; Rogers, S.; Crane, K.; Cywin, C.; Brown, M.; Pargellis, C. *Nat. Struct. Biol.* **1997**, *4*, 311. (e) Sicheri, F.; Moarefi, I.; Kuriyan, J. *Nature* **1997**, *385*, 602. (f) Filgueria-de-Azevedo, W., Jr.; Mueller-Dieckmann, H.-J.; Schulze-Gahmen, U.; Worland, P. J.; Sausville, E.; Kim, S.-H. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 2735. (g) Engh, R.; Girod, A.; Kinzel, V.; Huber, R.; Bossemeyer, D. *J. Biol. Chem.* **1996**, *271*, 26157. (h) Mohammadi, M.; McMahon, G.; Sun, L.; Tang, C.; Hirth, P.; Yeh, B.; Hubbard, S.; Schlessinger, J. *Science* **1997**, *276*, 955.

(5) For a recent review, see: Hinterding, K.; Alonso-Diaz, D.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 688 and references therein.

(6) For recent reviews, see: (a) Hofmann, J. *FASEB J.* **1997**, *11*, 649. (b) Myers, M. R.; Wei, H.; Hulme, C. *Curr. Pharm. Des.* **1997**, *3*, 473. (c) Bridges, A. J. *Emerging Drugs* **1998**, *3*, 279.

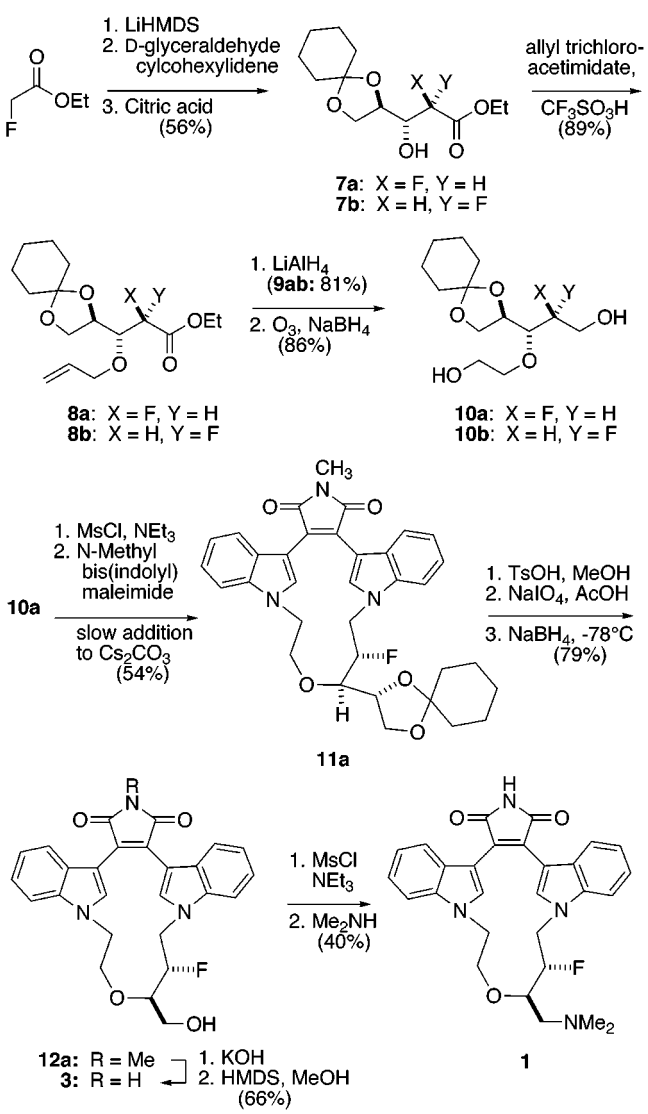
10.1021/jo9808876 CCC: $18.00 
Published on Web 05/18/1999

including cardiac hypertrophy, atherosclerosis, systemic lupus erythematosus, diabetes mellitus, Alzheimer's disease, malignant glioma, cancer, AIDS, and angiogenesis.[7,8] Most structural studies have focused on the unique regulatory domain of PKC,[9] as targeting the conserved catalytic domain might seem counterproductive. However, the fact that the catalytic domains can be discriminated suggests that a more detailed look at this site is warranted. Targeting the most common feature may offer a more general solution to protein kinase inhibition, and a detailed understanding of the structural basis for isoform-selective inhibition of the PKC catalytic domain by the macrocyclic bis(indolyl)maleimides may provide important insight for the design of selective inhibitors for other protein kinases.[6b,c]

A series of fluorine-labeled macrocyclic bis(indolyl)-maleimides **1**−**6** have therefore been prepared as potential fluorine-NMR probes for structural studies of the catalytic domain of PKC. Fluorine NMR is evolving as a powerful tool for protein studies as a result of high sensitivity, the absence of fluorine in the native protein, and the ability to detect fluorine−proton heteronuclear Overhauser effects.[10] One aspect that has not been exploited extensively to our knowledge is the potential for the use of vicinal fluorine−proton coupling constants to provide conformational information in protein-inhibitor complexes.[11] Vicinal $^3J(H,F)$ coupling constants are approximately three times larger than the corresponding proton−proton couplings (ca. 6−40 Hz) and can be measured directly in smaller complexes if the line widths are less than the couplings or indirectly through quantitative *J*-correlation experiments in larger systems where the couplings are unresolved.[12]

The compounds **1**−**6** bear a fluorine label on the macrocyclic ring. Tethering the bis(indolyl)maleimide within a macrocyclic ring was instrumental in achieving high potency and isoform selectivity.[13] Placing a fluorine label on the aliphatic portion of the macrocycle allows for experimental studies into the behavior of that portion of the macrocycle while bound to PKC. Such studies can provide more insight into the role of the macrocycle, such as whether the ring is bound by the protein or if it serves only to restrict the conformation of the bis(indolyl)-maleimide. The synthesis and biological activity of the macrocyclic fluorinated compounds are reported herein.

**Scheme 1**




## Results and Discussion

**Synthesis.** A flexible route was designed for access to enantiomerically pure compounds of the type **1**−**6**. The synthesis of **1** and **3** are shown in Scheme 1. A Welch aldol[14] condensation of ethyl fluoroacetate with (*R*)-glyceraldehyde cyclohexylidene[15] provided a 2:1 mixture of diastereomeric adducts **7a** and **7b** having the appropriate stereochemistry at C.2 and C.3. The poor stereoselectivity at the C.2 fluorine coupled with high diastereoselectivity at the C.3 hydroxyl was attractive because both diastereomers were needed for this study. In view of Welch's closely related result with D-glyceraldehyde acetonide, the stereochemistry of the C.3 hydroxyl was not in doubt. However, the low selectivity at

(7) For a review, see: Bradshaw, D.; Hill, C. H.; Nixon, J. S.; Wilkinson, S. E. *Agents Actions* **1993**, *38*, 135. See also: Wilkinson, S. E.; Hallam, T. J. *Trends Pharmacol. Sci.* **1994**, *15*, 53.

(8) (a) Wakasaki, H.; Koya, B.; Schoen, F. J.; Jirousek, M. R.; Ways, D. K.; Hoit, B. D.; Walsh, A.; King, G. L. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 9320. (b) Marche, P.; Herembert, T.; Zhu, D. L. *Int. J. Cardiol.* **1997**, *62*, S17. (c) Fernandez-Gutierrez, B.; de Miguel, S.; Morado, C.; Hernandez-Garcia, C.; Banares, A.; Jover, J. A. *Lupus* **1998**, *7*, 314. (d) Standaert, M. L.; Galloway, L.; Karnam, P.; Bandyopadhyay, G.; Moscat, J.; Farese, R. V. *J. Biol. Chem.* **1997**, *272*, 3075. (e) Benussi, L.; Govoni, S.; Casparini, L.; Binetti, G.; Trabucchi, M.; Bianchetti, A.; Racchi, M. *Neurosci. Lett.* **1998**, *240*, 97. (f) Bredel, M.; Pollack, I. F. *Acta Neurochir.* **1997**, *139*, 1000. (g) Blobe, G. C.; Stribling, S.; Obeid, L. M.; Hannun, Y. A. *Cancer Surv.* **1996**, *27*, 213. (f) Wyss-Coray, T.; Masliah, E.; Toggas, S. M.; Rockenstein E. M.; Brooker, M. J.; Lee, H. S.; Mucke, L. *J. Clin. Invest.* **1996**, *97*, 789. (g) Pal, S.; Claffey, K. P.; Cohen, H. T.; Mukhopadhyay, D. *J. Biol. Chem.* **1998**, *273*, 26277.

(9) See, for example: (a) Zhang, G.; Kazanietz, M. G.; Blumberg, P. M.; Hurley, J. H. *Cell* **1995**, *81*, 917. (b) Rouhi, A. M. *Chem. Eng. News* **1995**, *73*(43), 21. (c) Wender, P. A.; Irie, K.; Miller, B. L. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 239 and references therein. (e) Pap, E. H. W.; Vandenberg, P. A. W.; Borst, J. W.; Visser, A. J. W. *G. J. Biol Chem.* **1995**, *270*, 1254. (f) Rando, R. R.; Kishi, Y. *Biochemistry* **1992**, 31, 2211.

(10) Gerig, J. T. *Prog. Nucl. Magn. Reson. Spectrosc.* **1994**, *26*, 293.

(11) Thibaudeau, C.; Plavec, J.; Chattopadhyaya, J. *J. Org. Chem.* **1998**, *63*, 4967.

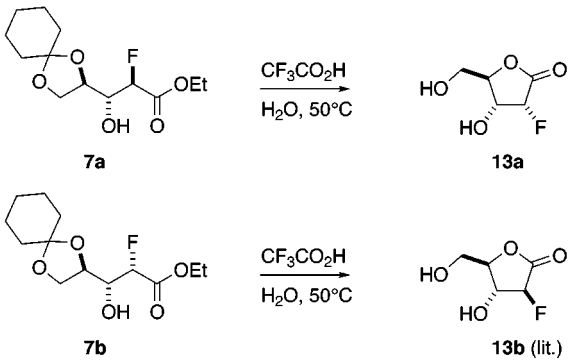
(12) Bax, A.; Vuister, G. W.; Grzesiek, S.; Delaglio, F.; Wang, A. C.; Tschudin, R.; Zhu, G. In *Methods in Enzymology*; James, T. L., Oppenheimer, N. J., Eds.; Academic Press: San Diego, 1994; Vol. 239, Chapter 2.

(13) The nonmacrocyclic bis(indolyl)maleimides as a class are less potent and less isoform-selective PKC inhibitors. For a review, see: Prudhomme, M. *Curr. Pharm. Design* **1997**, *3*, 265.

(14) Welch, J. T.; Eswarakrishnan, S. *J. Chem. Soc., Chem. Commun.* **1985**, 186.

(15) Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem.* **1995**, *60*, 585.

**Scheme 2**

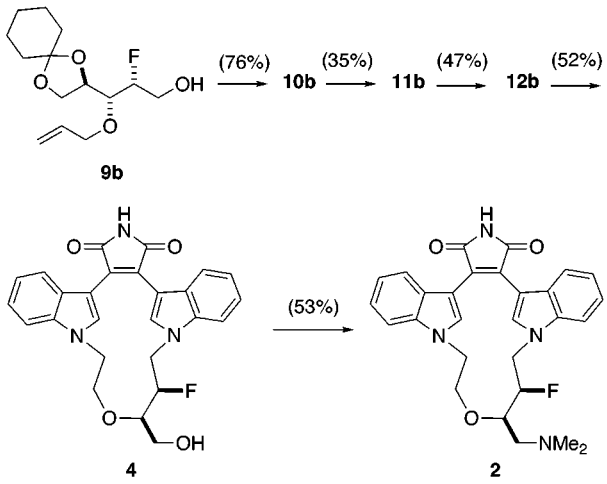



fluorine (1:1.2 in Welch's case) precluded an assignment of the stereochemistry based on a major vs minor isomer argument. The stereochemistry of the fluorine labels were therefore confirmed by chemical correlation of the isomer **7b** to 2-deoxy-2-fluoro-D-arabinono-1,4-lactone (Scheme 2).[16]

The synthesis beyond this stage follows a route similar to that published for LY333531.[17] Acid-catalyzed allylation of **7a,b** provided the esters **8a,b**, and lithium aluminum hydride reduction afforded the common intermediates **9a** and **9b**. In practice, although the aldol products could be separated with some effort as the trimethylsilyl ethers, it was most convenient to separate the diastereomers at the stage of the allylated esters or alcohols. NMR experiments with chiral shift reagents were performed to confirm the enantiomeric purity of the allylated ester **8a**.[18] Ozonolysis and sodium borohydride reduction of **9a** provided the diol **10a**. Coupling of the dimesylate of **10a** with *N*-methyl 2,3-bis[1*H*-indol-3-yl]-maleimide[19] by slow addition of both components to $Cs_2CO_3$ in DMF provided the macrocycle **11a**. Deprotection to the diol, periodate oxidation, and selective reduction[20] of the aldehyde in the presence of the maleimide moiety produced the alcohol **12a**. Removal of the maleimide *N*-methyl protecting group by hydrolysis to the anhydride followed by addition of HMDS−methanol according to the procedure of Davis[21] provided the primary alcohol **3**. Conversion of the primary alcohol to the dimethylamino group provided **1**, the fluorine-labeled analogue of LY333531. The diastereomeric fluorine-labeled compounds **2** and **4** were prepared by the same route starting from **9b** (Scheme 3).

The presence of the electronegative fluorine was a significant complicating factor when compared to the

**Scheme 3**




synthesis of the parent compound, as a result of both its propensity for elimination or displacement and its inductive effect on neighboring functional groups. Significant differences were observed between the two diastereomeric series, as the stereochemical arrangement of the electronegative fluorine was found to influence the chemistry. A notable decrease in yield was observed for the (*R*)-diastereomer in each of the steps involving the macrocyclic compounds. The coupling of the dimesylate of **10b** proceeded in consistently lower yield than that of the diastereomer **10a**; decomposition of the dimesylate has been previously shown to compete with coupling.[22] In addition, a higher propensity toward elimination of the fluoride and toward degradation of the maleimide was observed in this series during the reduction of the aldehyde to the alcohol **12b** and again in the hydrolysis of the *N*-methyl maleimide. Analysis of the vicinal coupling constants in the $^1$H NMR of the acyclic precursors indicate a marked difference in ground-state conformation.[23] It can be speculated that the cost of overcoming this difference in the macrocyclic compounds is reflected in the transition state of the macrocyclization reaction and as additional strain in the ground state of subsequent intermediates.

The 15-membered macrocyclic compounds **5** and **6** were prepared from the allylated alcohol **9a** as shown in Scheme 4. Hydroboration and mesylation led to the dimesylate **14**, which was coupled to *N*-methyl 2,3-bis-[1*H*-indol-3-yl]maleimide to provide **15**. Deprotection, periodate cleavage, and reduction were performed in the same manner as previously to provide the primary alcohol **16**. Conversion of the *N*-methyl maleimide to the free maleimide provides **5**. The primary alcohol was converted to the dimethylamino compound **6** in order to provide direct analogues in the 15- and 14-membered macrocycle series.

**Biological Activity.** The substitution of a hydrogen with fluorine can significantly impact the biological activity, and it is desirable to retain the high affinity of LY333531 for PKC-$\beta$ in order to use these compounds as NMR probes. The half-inhibitory concentrations ($IC_{50}$'s) in Table 1 indicate that the 14-membered ring compounds **1**−**3** remain potent (low nM) inhibitors of PKC-

(16) Bols, M.; Lundt, I. *Acta Chem. Scand.* **1990**, *44*, 252.

(17) Jirousek, M. R.; Gillig, J. R.; Gonzalez, C. M.; Heath, W. F.; McDonald, J. H.; Neel, D. A.; Rito, C. J.; Singh, U.; Stramm, L. E.; Melikianbadalian, A.; Baevsky, M.; Ballas, L. M.; Hall, S. E.; Winneroski, L. L.; Faul, M. M. *J. Med. Chem.* **1996**, *39*, 2664.

(18) The optical rotations of the macrocyclic bis(indolyl)maleimides are weak (ca 10°) and cannot be measured accurately because the compounds absorb at 598 nm. An NMR experiment was therefore performed as a measure of optical purity. At no point in the later synthesis are both chiral centers at risk; the experiment thus confirms the optical purity (>95:5) of the final products. Experimental procedure: a solution of the allylated ester (+)-**8a** (15.8 mg) in benzene-$d_6$ (900 mL) was divided into two equal portions. (+)-Eu(tfc)$_3$ (45.0 mg, [**8a**] = 0.056 M; [Eu(tfc)$_3$] = 0.112 M) was added to the first sample, and an equal amount of (−)-Eu(tfc)$_3$ was added to the second. The spectra obtained from the two samples were readily distinguishable, and no evidence of the complexes of the enantiomer of **8a** were observed. Spectra are provided in the Supporting Information.

(19) Brenner, M.; Rexhausen, H.; Steffan, B.; Steglich, W. *Tetrahedron* **1988**, *44*, 2887.

(20) Ward, D. E.; Rhee, C. K. *Synth. Comm.* **1988**, *18*, 1927.

(21) Davis, P. D.; Bit, R. A. *Tetrahedron Lett.* **1990**, *31*, 5201.

(22) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A.; Sullivan, K. A.; Gillig, J. R.; Neel, D. A.; Rito, C. J.; Jirousek, M. R. *J. Org. Chem.* **1998**, *63*, 1961.

**Scheme 4**

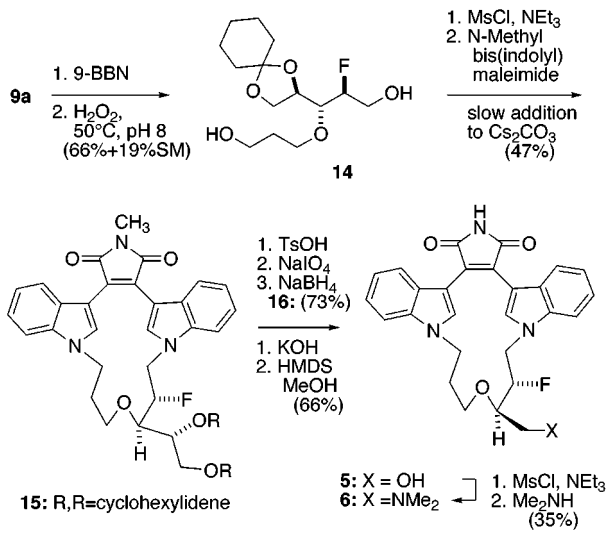



**Table 1. Inhibition Constants against PKC-$\beta$(II) for LY333531 and Fluorine-Labeled Compounds**

| entry | substrate | $IC_{50}$ (nM) |
|---|---|---|
| 1[a] | LY333531 | 2 |
| 2[b] | **1** | 1 |
| 3[b] | **1** | 2 |
| 4 | **2** | 2 |
| 5 | **3** | 3 |
| 6 | **5** | 13 |
| 7 | **6** | 90 |

[a] This assay. [b] Entries 2 and 3 represent different samples of **1** prepared independently.

$\beta$.[24] The relationship between $IC_{50}$'s, binding constants, and exchange rates is not straightforward, and the latter will ultimately have to be determined experimentally. However, the binding constant for LY333531 to PKC-$\beta$(II) has been measured at 2.5 nM,[1] and we may assume a similar relationship between $IC_{50}$'s and binding constants for the fluorinated case. With a binding constant of less than 5 nM, and barring an exceptionally fast on-rate, we expect the 14-membered rings to exhibit slow exchange on the NMR time scale. The 15-membered ring dimethylamine **6** appears to be less potent and may exhibit fast exchange on the NMR time scale, which would provide related probes in both the fast and slow exchange regimes.

**Fluorine NMR.** The apparent vicinal coupling constants between fluorine and hydrogen in these compounds range in magnitude from 6 to 35 Hz. The larger vicinal coupling constants, such as the apparent 35 Hz coupling between the fluorine and the C.1′ proton of compound **3**, should be possible to determine in a complex with the catalytic domain of PKC. It is interesting that the analogous coupling constant is 20 Hz in the dimethylamine **1**, indicating a substantially different solution conformation for the dimethylamine from that of the preceding synthetic intermediates. The fact that the analogue of LY333531 **1** has a unique solution conformation suggests that determining the conformation of these compounds while bound to PKC may be a useful objective.

## Conclusions

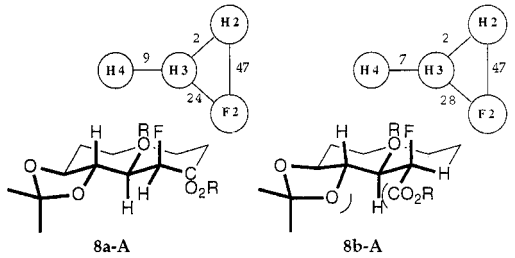
A series of fluorine-labeled macrocyclic bis(indolyl)-maleimides have been prepared. These compounds retain a strong affinity for PKC as evidenced by low nanomolar $IC_{50}$'s. The vicinal proton−fluorine coupling constants correlate to the local macrocycle conformation and can be used to determine the bound conformation, provided that they can be measured by quantitative *J* correlation in the protein complex. More detailed biological and solution conformational studies are currently underway and will be reported separately.

## Experimental Section

**General Experimental.** THF and toluene were dried by distillation from sodium−potassium/benzophenone ketyl; HMPA and HMDS by distillation from $CaH_2$; methanol by distillation from magnesium methoxide; and DMF by distillation from ninhydrin and calcium hydride. Proton and carbon chemical shifts at 292 ± 2 K are reported relative to TMS using either TMS or the residual solvent signal as internal standard. Carbon NMRs are proton-decoupled, and coupling constants to fluorine are reported. Only selected signals are provided, and complete listings are available in the Supporting Information. Fluorine chemical shifts at 292 ± 2 K are reported relative to $CCl_3F$ using $C_6F_6$ (−163.0 ppm) as an external standard. Fluorine spectra were collected for each sample with windows of 50 000 and 5 000 Hz. All coupling constants are apparent coupling constants measured directly from the 1-D NMR spectrum.

**PKC-$\beta$(II) Assays.** Assays were performed as reported previously,[17] with the following modifications. Assays were performed in a total volume of 100 $\mu$L in 96 well plates. Components are as follows: 10 $\mu$L 9.4 mM $Ca^{2+}$; 55 $\mu$L lipids in HEPES pH 7.5 buffer (PS: 5 $\mu$g/well, DAG: 6 $\mu$g/well); 5 $\mu$L solution of compound in DMSO; 10 $\mu$L substrate (MBP 3 mg/mL); and 10 $\mu$L $^{32}$P-ATP (300 $\mu$M ATP, 0.25 $\mu$Ci/well, and 10 mM $MgCl_2$). The assay was started with the addition of 10 $\mu$L PKC-$\beta$(II) solution in HEPES pH 7.5 buffer. The assays were run for 10 min at 30 °C, and the reaction was terminated with 100 $\mu$L of cold 25% TCA and 25 $\mu$L of 1 mg/mL BSA. An aliquot of the mixture was transferred to a 96 well glass fiber plate, filtered, and washed three times with cold 10% TCA. A 100 $\mu$L portion of Microscint/20 (Packard) was added, and the plates were counted in a Packard Top Count. Each $IC_{50}$ value

(23) The diasteriomeric allylated aldol products **8a** and **8b** have similar vicinal coupling patterns, reflecting different dominant conformations **8a-A** and **8b-A** for the two series. The principal conformational feature is a gauche arrangement between the electronegative fluorine and oxygen atoms. The conformation around the C.3−C.4 bond is also consistent with the assigned behavior. Whereas the coupling between H.3 and H.4 in **8a** shows an extended conformation with the two protons antiperiplanar, there is some distortion around the C.3−C.4 bond in **8b**. This is consistent with a synpentane interaction between the C.4 oxygen and the ester functionality in conformation **8b-A**. The coupling constants in the primary alcohols **9a,b** and diols **10a,b** reflect a similar conformational behavior, with the oxygens gauche to the fluorine in both series.




(24) Preliminary experiments on PKC-α suggest that compound **1** has an isoform selectivity comparable to that of LY333531, whereas compound **2** is slightly more selective and compound **3** is substantially less so. Additional studies on the isoform selectivity are underway. Experiments on alcohol **4** also point to an $IC_{50}$ of 5 nM against PKC-$\beta$ (75% inhibition at 9.8 nM) and weak isoform selectivity.

was determined once from five concentrations of inhibitor (0.5−5000 nM).

**Ethyl (2*R*,3*R*)- and (2*S*,3*R*)-3-[(2*R*)-1,4-Dioxaspiro[4.5]-decanyl]-2-fluoro-3-hydroxypropanoate (7a,b).** A stirred solution of hexamethyldisilazane (5.0 mL, 0.0255 mol) in anhydrous THF (40 mL) at 0 °C under $N_2$ was treated with *n*-butyllithium (2.5 M solution in hexane, 9.0 mL, 0.0225 mol). After 10 min of stirring at room temperature, the mixture was cooled to −78 °C[25] and treated with HMPA (3.6 g, 0.020 mol) and ethyl fluoroacetate (2.0 mL, 0.020 mol, added dropwise in 5 min). After an additional 5 min of stirring at −78 °C, freshly distilled cyclohexylidene-D-glyceraldehyde (760 mg, 4.46 mmol) was added quickly. The mixture was allowed to stir for 10 min and was quenched at −78 °C with saturated $NH_4Cl$. The mixture was extracted with hexane and chloroform, and the organic layers were washed with saturated $NH_4Cl$ and dried over $Na_2SO_4$. After evaporation under reduced pressure, the residue was chromatographed twice on silica gel using 30% ethyl acetate−hexane, yielding the *O*-trimethylsilylated aldol product[26] (740 mg) and the aldol product **7a,b** (92 mg), both as 3:1 mixtures of diastereomers on the basis of $^1$H NMR. The silylated material (740 mg, 2.10 mmol) was dissolved in $CH_3OH$ (60 mL), treated with citric acid (1.2 g), and stirred at room temperature for 4 h. The solvent was removed under reduced pressure, and the residue was taken up with ethyl acetate and washed with saturated $NaHCO_3$ and water. The ethyl acetate layer was dried over $Na_2SO_4$ and evaporated, yielding 600 mg of **7a,b**, (2.10 mmol; 692 mg combined yield of the aldol product, 2.51 mmol, 56%) as a clear colorless oil. Analytical samples of the pure isomers **7a** and **7b** were obtained from the mixture of trimethylsilylated products by repeated chromatography on silica gel eluted with $CHCl_3$, followed by hydrolysis under the conditions above. HRMS (EI): calculated for $C_{13}H_{21}FO_5$ 276.1373, observed 276.1369. **7a (2*R*):** FTIR (neat film): 3458 cm$^{-1}$, 1766, 1743. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.15 ppm (1H, dd, $J$ = 48.3, 2.3 Hz); 4.30 (2H, m, $J$ = 7.2 Hz); 4.20 (1H, ddd, $J$ = 7.9, 5.8, 5.1 Hz); 4.15−4.00 (3H); 2.60 (1H, br. d); 1.34 (3H, t, $J$ = 7.2 Hz). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 167.2 ppm (d, $J$ = 24.0 Hz); 110.3; 89.9 (d, $J$ = 186.6 Hz); 73.7 (d, $J$ = 5.9 Hz); 73.1 (d, $J$ = 21.0 Hz); 66.1; 61.8; 36.4; 34.5; 25.1; 24.0; 23.7; 14.1. $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −202.4 ppm (dd, $J$ = 48.0, 23.3 Hz). $[\alpha]^{25}_D$ +1.3° (*c* 2.50 $CHCl_3$). **7b (2*S*):** FTIR (neat film): 3456 cm$^{-1}$, 1766, 1743. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.18 ppm (1H, dd, $J$ = 47.3, 1.4 Hz); 4.31 (2H, q, $J$ = 7.2 Hz); 4.20−3.84 (4H); 2.36 (1H, br. d, $J$ = 8.8 Hz); 1.33 (3H, t, $J$ = 7.2 Hz). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 168.1 ppm (d, $J$ = 24.4 Hz); 110.4; 88.3 (d, $J$ = 187.6 Hz); 74.0 (d, $J$ = 3.7 Hz); 72.8 (d, $J$ = 17.7 Hz); 66.3; 62.0; 36.6; 34.6; 25.1; 24.0; 23.7; 14.1. $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −212.4 ppm (dd, $J$ = 48.0, 23.3 Hz). $[\alpha]^{25}_D$ +4.3° (*c* 1.62 $CHCl_3$).

**Stereochemistry Assignment: 2-Deoxy-2-fluoro-D-ribono-1,4-lactone and 2-Deoxy-2-fluoro-D-arabinono-1,4-lactone (13a,b).** The aldol product **7a** (68 mg, 0.25 mmol) was treated with trifluoroacetic acid−water (9:1, 4 mL) at 50 °C under nitrogen. The mixture was stirred for 14 h and concentrated at reduced pressure. The residue was evaporated azeotropically with a toluene−ethanol (5:1) mixture three times and then purified on a short silica gel column using ethyl acetate to yield the hydrolytically unstable lactone **13a** (10 mg, 0.067 mmol, 27% yield). The epimeric aldol **7b** (32 mg, 0.092 mmol) was converted to the lactone **13b** (7 mg, 0.047 mmol, 51% yield) by the same procedure. The lactone **13b** is identical to 2-deoxy-2-fluoro-D-arabinono-1,4-lactone by $^{13}$C NMR. **13a:** $^1$H NMR (300 MHz, $D_2O$, ref. acetone, 2.22 ppm ): $\delta$ 5.58 ppm (1H, dd, $J$ = 48.5, 5.4 Hz); 4.50−4.48 (1H, m); 4.47 (1H, d, $J$ = 5.5 Hz); 3.71(1H, dd, $J$ = 13.2, 2.8 Hz); 3.65 (1H, dd, $J$ = 13.2, 3.2 Hz). $^{13}$C NMR (100 MHz, $D_2O$, ref. dioxane, 67.4 ppm): $\delta$ 174.8 ppm (d, $J$ = 22 Hz); 88.0 (d, $J$ = 5 Hz); 86.7 (d, $J$ = 188 Hz); 69.2 (d, $J$ = 15 Hz); 60.9. **13b:** $^{13}$C NMR (100 MHz, $D_2O$, ref. dioxane, 67.4 ppm): $\delta$ 172.5 ppm (d, $J$ = 23 Hz); 92.7 (d, $J$ = 195 Hz); 81.7 (d, $J$ = 9 Hz); 71.6 (d, $J$ = 20 Hz); 60.0.

**Ethyl (2*R*,3*R*)- and (2*S*,3*R*)-3-(Allyloxy)-3-[(2*R*)-1,4-dioxaspiro[4.5]decanyl]-2-fluoropropanoate (8a,b).** A solution of the aldol products **7a,b** (655 mg, 2.37 mmol, a mixture of diastereomers) and allyl trichloroacetimidate (1.50 mL, 9.8 mmol) in cyclohexane (30 mL) was treated with $CF_3SO_3H$ (100 $\mu$L, 1.13 mmol, dropwise over 30 min). The reaction mixture was stirred at room temperature under $N_2$ for 46 h. Additional $CF_3SO_3H$ (60 $\mu$L, 0.68 mmol) was added, and the reaction mixture was stirred for another 24 h. The precipitate was filtered and washed with cyclohexane. The filtrate was evaporated, and the residue was chromatographed on silica gel using 10% ethyl acetate−hexane as eluent, yielding **8a** (511 mg, 1.62 mmol, 68%) and **8b** (160 mg, containing a small amount of **8a**, 0.506 mmol, 21%) as clear colorless oils. **8a (2*R*):** HRMS (EI): calculated for $C_{16}H_{25}FO_5$ 316.1686, observed 316.1678. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.87 ppm (1H, dddd, $J$ = 17.3, 10.4, 5.8, 5.8 Hz); 5.28 (1H, dd, $J$ = 17.3, 1.5 Hz); 5.23 (1H, dd, $J$ = 48.0, 1.2 Hz); 5.21 (1H, dd, $J$ = 10.3, 1.6 Hz); 4.35−4.20 (4H); 4.13−4.04 (2H); 3.93 (1H, dd, $J$ = 8.8, 4.5 Hz); 3.78 (1H, ddd, $J$ = 23.2, 8.5, 1.2 Hz); 1.33 (1H, t, $J$ = 7.2 Hz). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 167.4 ppm (d, $J$ = 23.0 Hz); 89.4 (d, $J$ = 189.4 Hz); 80.5 (d, $J$ = 19.8 Hz); 73.0 (d, $J$ = 7.8 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −196.7 ppm (dd, $J$ = 48.0, 22.6 Hz). $[\alpha]^{25}_D$ +6.7° (*c* 1.74 $CHCl_3$). **8b (2*S*):** HRMS (EI): calculated for $C_{16}H_{25}FO_5$ 316.1686, observed 316.1691. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.82 ppm (1H, dddd, $J$ = 17.2, 10.4, 5.6, 5.6 Hz); 5.24 (1H, dd, $J$ = 17.2, 1.6 Hz); 5.17 (1H, dd, $J$ = 10.4, 1.6 Hz); 5.11 (1H, dd, $J$ = 47.2, 1.9 Hz); 4.40−4.20 (4H); 4.18−4.05 (2H); 3.99 (1H, dd, $J$ = 8.2, 5.4 Hz); 3.91 (1H, ddd, $J$ = 25.8, 7.1, 1.9 Hz); 1.34 (3H, t, $J$ = 7.2 Hz). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 168.3 ppm (d, $J$ = 23.8 Hz); 139.2; 117.5; 88.3 (d, $J$ = 191.5 Hz); 79.2 (d, $J$ = 18.3 Hz); 74.0 (d, $J$ = 3.5 Hz); 66.0 (d, $J$ = 1.8 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −208.6 ppm (dd, $J$ = 47.4, 27.5 Hz). $[\alpha]^{25}_D$ +1.7° (*c* 1.74 $CHCl_3$).

**(2*S*,3*R*)- and (2*R*,3*R*)-3-(Allyloxy)-3-[(2*R*)-1,4-dioxaspiro-[4.5]decanyl]-2(*R*,*S*)-fluoropropan-1-ol (9a,b).** The ester **8a** (635 mg, 2.00 mmol, containing a small amount of the diastereomer **8b**) in anhydrous THF (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (200 mg, 5.27 mmol, 2.5 equiv) in anhydrous THF (40 mL) at −78 °C under $N_2$. The reaction mixture was stirred for 20 min at −78 °C and 20 min at 0 °C. The reaction was quenched with ethyl acetate (5 mL), followed by 4 g wet sodium sulfate. The mixture was stirred for 30 min, and the solid was filtered away and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel using 30% ethyl acetate−hexane as eluent to yield the starting material **8a** (19 mg, 3% recovery), alcohol **9a** (413 mg, 1.51 mmol, 75% yield), and alcohol **9b** (30 mg, 0.11 mmol, 6% yield) as clear colorless oils. **9a (2*S*):** HRMS (EI): calculated for $C_{14}H_{23}FO_4$ 274.1580, observed 274.1575. FTIR (neat film): 3420 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.88 ppm (1H, dddd, $J$ = 17.2, 10.3, 5.8, 5.8 Hz); 5.27 (1H, dd, $J$ = 17.2, 1.0 Hz); 5.20 (1H, dd, $J$ = 10.3, 1.0 Hz); 4.72 (1H, dddd, $J$ = 47.4, 5.7, 3.5, 3.5 Hz); 4.25 (1H, dd, $J$ = 12.5, 5.7 Hz); 4.20−4.03 (3H); 4.03−3.80 (3H); 3.73 (1H, ddd, $J$ = 15.1, 6.7, 3.6 Hz); 2.30 (1H, br dd). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 134.1 ppm; 117.8; 93.6 (d, $J$ = 174 Hz); 78.0 (d, $J$ = 20.0 Hz); 74.2 (d, $J$ = 7.5 Hz); 61.8 (d, $J$ = 22.1 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −198.0 ppm (dddd, $J$ = 49, 24.5, 24.5, 15.4 Hz). $[\alpha]^{25}_D$ +5.8° (*c* 2.02 $CHCl_3$).

The ester **8b** (1.24 g, 3.92 mmol, containing a small amount of the diastereomer **8a**) was converted to the alcohols **9b** (534 mg, 1.95 mmol, 50% yield) and **9a** (151 mg, 0.55 mmol, 14% yield) by the same procedure. **9b (2*R*):** HRMS (EI): calculated for $C_{14}H_{23}FO_4$ 274.1580, observed 274.1576. FTIR (neat film): 3437 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 5.89 ppm (1H, dddd, $J$ = 17.2, 10.4, 5.8, 5.8 Hz); 5.28 (1H, dd, $J$ = 17.2, 1.5 Hz); 5.20 (1H, dd, $J$ = 10.4, 1.5 Hz); 4.63 (1H, dddd, $J$ = 47.1, 5.3,

(25) It is important to let the LHMDS solution stand for 30 min until it reaches −78 °C. At higher temperatures, higher diasterioselectivities but much lower yields were obtained.

(26) The aldol products were obtained as mixtures of the silylated and nonsilylated aldol products in highly variable ratios, from exclusively silylated to exclusively nonsilylated. We were unable to determine convincingly the experimental parameters responsible.

4.4, 4.4 Hz); 4.23−4.08 (4H); 4.02−3.75 (3H); 3.64 (1H, ddd, $J$ = 10.8, 6.2, 4.7 Hz); 2.41 (1H, br s). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 134.1 ppm; 117.7; 94.7 (d, $J$ = 174.7 Hz); 78.5 (d, $J$ = 18.4 Hz); 74.8 (d, $J$ = 5.9 Hz); 62.1 (d, $J$ = 23.9 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −199.0 ppm (dddd, $J$ = 46.4, 22.4; 22.4; 13.8 Hz). $[\alpha]^{25}_D$ +6.3° ($c$ 1.14 $CHCl_3$).

**(2*S*,3*R*)- and (2*R*,3*R*)-3-[(2*R*)-1,4-Dioxaspiro[4.5]decanyl]-2-fluoro-3-(2-hydroxyethoxy)propan-1-ol (10a,b).** The alcohol **9a** (387 mg, 1.41 mmol) was dissolved in $CH_3OH$−$CH_2Cl_2$ (1:1, 25 mL). The solution was cooled to −78 °C, and ozone was bubbled through until a blue color began to appear. Argon was bubbled in to remove excess $O_3$, five drops of $CH_3SCH_3$ were added, and the solution was stirred for 10 min. $NaBH_4$ (320 mg, 8.46 mmol) was added at −78 °C. After 10 min of stirring, the reaction mixture was allowed to return to room temperature and was stirred for 1 h. The mixture was treated with methanol (10 mL) and sodium potassium tartrate (10 mL saturated aqueous) and stirred overnight. The reaction mixture was concentrated down to remove methanol, diluted with water (30 mL), and extracted with methylene chloride (4 × 15 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure, and the residue was chromatographed on a silica gel column using ethyl acetate as eluent, yielding **10a** (339 mg, 1.22 mmol, 86% yield) as a clear colorless oil. **10a (2*S*):** HRMS (EI): calculated for $C_{13}H_{23}FO_5$ 278.1530, observed 278.1534. FTIR (neat film): 3398 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.55 ppm (1H, dddd, $J$ = 47.0, 5.0, 4.4, 3.5 Hz); 4.26 (1H, dddd, $J$ = 6.2, 6.2, 6.2, 1.0 Hz); 4.06 (1H, dd, $J$ = 7.8, 6.7 Hz); 4.00−3.75 (6H); 3.75−3.65 (2H, m); 3.2 (2H, br. s). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 93.1 ppm (d, $J$ = 172.5 Hz); 78.5 (d, $J$ = 21.5 Hz); 74.7(d, $J$ = 5.2 Hz); 61.5 (d, $J$ = 21.5 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −197.4 ppm (dddd, $J$ = 48.3, 26.2, 23.6, 13.0 Hz). $[\alpha]^{25}_D$ 1.8° ($c$ 2.0 $CHCl_3$).

The diastereomer **9b** (470 mg, 1.71 mmol) was converted to the diol **10b** (362 mg, 1.30 mmol, 76% yield) in the same manner. **10b (2*R*):** HRMS (EI): calculated for $C_{13}H_{23}FO_5$ 278.1530, observed 278.1537. FTIR (neat film): 3437 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.61 ppm (1H, dddd, $J$ = 46.6, 5.4, 5.3, 3.3 Hz); 4.22 (1H, ddd, $J$ = 6.5, 6.5, 4.9 Hz); 4.10−3.65 (9H); 3.40 (2H, br. s). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 93.3 ppm (d, $J$ = 175.5 Hz); 78.5 (d, $J$ = 17.9 Hz); 75.6 (d, $J$ = 3.8 Hz); 65.1 (d, $J$ = 4.6 Hz); 60.8 (d, $J$ = 26.4 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −202.3 ppm (dddd, $J$ = 46.4, 25.6, 18.8, 18.8 Hz). $[\alpha]^{25}_D$ +3.3° ($c$ 1.5 $CHCl_3$).

**(18*R*,19*S*)- and (18*R*,19*R*)-18-[(2*R*)-1,4-Dioxaspiro[4.5]-decanyl]-19-fluoro-4-methyl-17-oxa-4,14,21-triazahexacyclo[19.6.1.1$^{7,14}$.0.$^{2,6}$.0$^{8,13}$.0$^{22,27}$]nonacosa-1(28),2(6),7(29),8,10,12,22(27),23,25-nonaene-3,5-dione (11a,b).** A solution of the diol **10a** (195 mg, 0.700 mmol) in diethyl ether (50 mL) was treated with triethylamine (583 $\mu$L, 4.2 mmol) and methanesulfonyl chloride (342 $\mu$L, 4.2 mmol). The mixture was stirred at room temperature under $N_2$ for 3 h. The reaction was quenched with water (50 mL), and the ether layer was separated and washed twice with water. After drying over anhydrous $Na_2SO_4$, the solution was concentrated at reduced pressure to yield the crude dimesylate as a yellowish oil (308 mg, quantitative).

To a suspension of cesium carbonate (768 mg, 2.36 mmol) in DMF (40 mL) at 50 °C under $N_2$ was added a solution of the crude dimesylate (257 mg, 0.59 mmol) and 2,3-bis[1*H*-indol-3-yl]-*N*-methylmaleimide (202 mg, 0.59 mmol) in DMF (10 mL) via syringe pump over a period of 48 h. The reaction mixture was diluted with 100 mL of $CHCl_3$ and washed with brine and then water. The chloroform layer was dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using 5% acetone−$CHCl_3$ as eluent to yield **11a** (185 mg, 0.317 mmol, 54% yield) as a purple solid. **11a (19*S*):** HRMS (FAB): calculated for $C_{34}H_{34}FN_3O_5$ + Na 606.2380, observed 606.2360. FTIR (neat film): 1697 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.07 ppm (1H, m); 7.94 (1H, dd, $J$ = 7.3, 0.8 Hz); 7.35 (1H, dd, $J$ = 8.0, 8.0 Hz); 7.33−7.20 (8H); 4.88 (C-2′, 1H, dddd, $J$ = 43.2, 4.7, 4.6, 2.3 Hz); 4.64 (C.1′, 1H, ddd, $J$ = 33.7, 15.8, 2.3 Hz); 4.30 (C.1′, 1H, ddd, $J$ = 15.8, 11.5, 4.7 Hz); 4.28 (C.7′, 1H, ddd, $J$ = 10.8, 3.9, 3.1 Hz); 4.07−3.88 (4H); 3.85−3.67 (3H); 3.23 (3H, s). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 171.5 ppm; 171.4; 136.9; 136.0; 133.1; 131.4; 131.2; 130.5; 130.4; 126.9; 126.9; 122.7; 122.4 (C-4); 122.2 (C-4); 121.9; 121.1; 121.0; 110.4; 109.1; 108.9; 105.9; 104.6; 91.5 (d, $J$ = 178.8 Hz); 80.7 (d, $J$ = 19.2 Hz); 74.2 (d, $J$ = 6.7 Hz); 72.0; 66.6; 46.3; 46.3 (d, $J$ = 25.6 Hz); 36.2; 34.2; 25.0; 24.1; 24.0; 23.8. $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −191.1 ppm (ddddd, $J$ = 43, 35; 9, 9, 3 Hz). $[\alpha]^{25}_D$ + 23° ($c$ 0.21 $CHCl_3$). UV−vis $\lambda_{max}$: 282, 372, 490 nm.

The fluorine diastereomer dimesylate of diol **10b** (46 mg, 0.107 mmol) was converted to the fluorinated macrocyclic bis-(indolyl)maleimide **11b** (19 mg, containing ca. 10% of inseparable contaminants, 0.039 mmol, 35% yield from **10b**) by the same procedure, except that the addition was performed at 100 °C over 6 h. **11b (19*R*):** HRMS (FAB): calculated for $C_{34}H_{34}FN_3O_5$ + Na 606.2380, observed 606.2361. FTIR (neat film): 1703 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.99 ppm (2H, d, $J$ = 7.6 Hz); 7.43 (1H, d, $J$ = 8.0 Hz); 7.40−7.20 (5H); 7.13 (1H, s); 7.11 (1H, s); 4.85 (1H, dddd, $J$ = 42.1, 9.5, 3, 2 Hz); 4.70 (1H, ddd, $J$ = 14.5, 9.5, 5.0 Hz); 4.37−4.17 (2H); 4.15−3.95 (3H); 3.90 (2H, m); 3.75−3.60 (2H); 3.23 (3H, s). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 171.3 ppm; 135.9; 132.6; 131.8; 130.5; 129.7; 127.0; 126.8; 122.8; 122.5; 122.1; 121.3; 121.2; 110.3; 109.3; 109.0; 105.7; 104.5; 90.2 (d, $J$ = 179.9 Hz); 78.7 (d, $J$ = 22.7 Hz); 74.4; 68.9; 66.3 (d, $J$ = 2 Hz); 45.9; 45.1 (d, $J$ = 34.0 Hz); 36.1; 34.2; 25.0; 24.0; 23.8 $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −184.74 ppm (m). UV−vis $\lambda_{max}$: 282, 372, 492 nm.

**(18*R*,19*S*)- and (18*R*,19*R*)-19-Fluoro-18-(hydroxymethyl)-4-methyl-17-oxa-4,14,21-triazahexacyclo[19.6.1.1$^{7,14}$.0.$^{2,6}$.0$^{8,13}$.0$^{22,27}$]nonacosa-1(28),2(6),7(29),8,10,12,22(27),23,25-nonaene-3,5-dione (12a,b).** The starting material **11a** (69 mg, 0.114 mmol) in methanol (50 mL) was treated with *p*-toluenesulfonic acid monohydrate (1.0 g). The reaction mixture was refluxed for 2 h. It was evaporated on a rotary evaporator, and the residue was diluted with methylene chloride (50 mL) and washed with $NaHCO_3$. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate as eluent to yield the diol as a deep purple solid (60 mg).

A 55 mg portion of the above diol was dissolved in a mixture of acetone and acetic acid (1:1, 20 mL). A solution of sodium metaperiodate (100 mg, 0.373 mmol) in water (2.5 mL) was added at room temperature, and the mixture was stirred for 2.5 h. The reaction was concentrated to half its original volume, diluted with methylene chloride (30 mL), and washed with water, $NaHCO_3$, and water. The organic layer was dried over $Na_2SO_4$ and evaporated to dryness, yielding the crude aldehyde.

A solution of the crude aldehyde in $CH_2Cl_2$ (14 mL) and ethanol (3 mL) at −78 °C was treated with a fresh suspension[27] of $NaBH_4$ (30 mg, 0.793 mmol) in ethanol (3 mL). The mixture was stirred at −78 °C for 40 min and quenched with 500 $\mu$L of acetaldehyde. The reaction mixture was allowed to return to room temperature, concentrated to half its original volume, and treated with 10 mL of ethanol and 2 mL of saturated KNa tartrate. The reaction was stirred for 5 h, concentrated under reduced pressure, and diluted with 30 mL $CH_2Cl_2$. The reaction was washed three times with water. The organic layer was dried over $Na_2SO_4$ and evaporated, and the residue was chromatographed on silica gel eluted with 10% EtOAc−$CH_2Cl_2$ and then EtOAc, yielding the fluoride elimination product (7 mg, 14%) and the desired alcohol **12a** (41 mg, 0.0826 mmol, 79% yield) as a purple solid. **12a (19*S*):** HRMS (FAB): calculated for $C_{27}H_{24}FN_3O_4$ + Na: 496.1649, observed 496.1653. FTIR (neat film): 3461 cm$^{-1}$, 1703. $^1$H NMR (300 MHz, acetone-$d_6$): $\delta$ 8.05 ppm (1H, dd, $J$ = 7.6, 1.0 Hz); 7.89 (1H, dd, $J$ = 7.7, 1.1 Hz); 7.56 (1H, s); 7.51 (1H, d, $J$ = 8.1 Hz); 7.47 (1H, d, $J$ = 8.0 Hz); 7.40 (1H, s); 7.30−7.10 (4H), 4.95 (1H, dddd, $J$ = 43.9, 7.3, 5.3; 2.0 Hz); 4.62 (1H, ddd, $J$ = 15.5, 9.7, 5.3 Hz); 4.56−4.35 (3H); 4.02 (2H, m); 3.86 (1H, m); 3.67

(27) It is important to add the borohydride suspension within 1 min of preparing it. Allowing the suspension to stand for 15 min was found to decrease the yield.

(1H, dddd, $J$ = 7.6, 7.4, 3.1, 3.1 Hz); 3.51 (1H, dddd, $J$ = 12.5, 6.1, 3.2, 3.1 Hz); 3.12 (3H, s). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 89.1 ppm (d, $J$ = 175.5 Hz); 78.9 (d, $J$ = 25.9 Hz); 66.8; 59.0 (d, $J$ = 5.5 Hz); 48.6 (d, $J$ = 27.0 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −185.9 ppm (dddd, $J$ = 41, 34, 9, 7 Hz). $[\alpha]^{25}_D$ +34° ($c$ 0.172 $CHCl_3$). UV−vis $\lambda_{max}$: 282, 370, 452 nm.

The (2*R*) diastereomer **11b** (60.3 mg, 0.103 mmol) was converted to the corresponding diol (39.6 mg, 37.0 mg carried on) then to the primary alcohol **12b** (21.5 mg, 0.0455 mmol, 47% yield for three steps) in the same manner. **12b (19*R*):** HRMS (FAB): calculated for $C_{27}H_{24}FN_3O_4$+Na: 496.1649, observed: 496.1661. FTIR (neat film): 3453 cm$^{-1}$, 1703. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.05−7.95 ppm (2H); 7.40−7.20 (6H); 7.20 (1H, s); 7.17 (1H, s); 4.95 (1H, dddd, $J$ = 42.9, 8.5, 3.3, 3.3 Hz); 4.52 (1H, ddd, $J$ = 14.8; 8.5, 5.7 Hz); 4.40−4.20 (2H); 4.10 (1H, m); 4.00 (1H, ddd, $J$ = 10.3, 9.1, 1.5 Hz); 3.86 (1H, m); 3.80−3.60 (3H); 3.20 (3H, s). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 90.2 ppm (d, $J$ = 176.4 Hz); 78.6 (d, $J$ = 25.3 Hz); 67.6; 60.0 (d, $J$ = 2.5 Hz); 46.1 (d, $J$ = 33.0 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −187.2 ppm (dddd, $J$ = 43, 15, 12, 6 Hz). UV−vis $\lambda_{max}$: 282, 374, 498 nm.

**(18*R*,19*S*)- and (18*R*,19*R*)-19-Fluoro-18-(hydroxymethyl)-17-oxa-4,14,21-triazahexacyclo[19.6.1.1$^{7,14}$.0.$^{2,6}$.0$^{8,13}$.0$^{22,27}$]-nonacosa-1(28),2(6),7(29),8,10,12,22(27),23,25-nonaene-3,5-dione (3 and 4).** A solution of **12a** (50 mg, 0.106 mmol) in $C_2H_5OH$ (3 mL) and 5 N KOH (3 mL) was stirred at 70 °C for 20 h. The solution was cooled to 0 °C and acidified with 5 N HCl. A red precipitate appeared. After 10 min of stirring, the mixture was extracted with methylene chloride and washed with water. Drying over $Na_2SO_4$, evaporation, and silica gel chromatography in 5% ethyl acetate−hexane yields the anhydride (33 mg, 0.0717 mmol, 68% yield) and recovered starting material (2.5 mg, 5%).

The anhydride (54 mg, 0.117 mmol) in DMF (5 mL) was treated with 1,1,1,3,3,3-hexamethyldisilazane (500 $\mu$L, 2.36 mmol) and $CH_3OH$ (48 $\mu$L, 0.62 mmol). The resulting mixture was stirred at room temperature under $N_2$ for 36 h. The volatiles were removed under reduced pressure. The residue was dissolved in 6 mL of $CH_3CN$−1 N HCl (2:1) and stirred at room temperature for 1 h. The organic solvent was removed, and the suspension was extracted with methylene chloride and washed with water and brine. The residue was dried over $Na_2SO_4$, concentrated, and separated on silica gel column eluted with 9:1 $CH_3CN$−$CH_2Cl_2$ to yield the imide **3** (31 mg) and recovered anhydride (20 mg). The recovered anhydride was resubmitted to the same reaction conditions to yield an additional 18 mg of **3** (combined 49 mg, 0.107 mmol, 91% yield; 66% for two steps) as a purple solid. **3 (19*S*):** HRMS (FAB): calculated for $C_{26}H_{22}FN_3O_4$ + H 460.1672, observed 460.1655. FTIR (neat film): 3450 cm$^{-1}$, 1697. $^1$H NMR (300 MHz, acetone-$d_6$): $\delta$ 9.72 ppm (1H, s); 8.04 (1H, dd, $J$ = 7.6, 1.0 Hz); 7.89 (1H, dd, $J$ = 7.7, 1.1 Hz); 7.56 (1H, s); 7.51 (1H, d, $J$ = 8.1 Hz); 7.49 (1H, d, $J$ = 8.0 Hz); 7.40 (1H, s); 7.30−7.10 (4H), 4.95 (1H, dddd, $J$ = 43.8, 7.2, 5.3; 2.1 Hz); 4.62 (1H, ddd, $J$ = 15.4, 9.8, 5.4 Hz); 4.56−4.35 (3H); 4.02 (2H, m); 3.86 (1H, m); 3.68 (1H, dddd, $J$ = 7.6, 7.4, 3.1, 3.1 Hz); 3.51 (1H, dddd, $J$ = 12.5, 6.1, 3.2, 3.1 Hz). $^{13}$C NMR {H} (125 MHz, $CD_2Cl_2$): _ 89.8 ppm (d, $J$ = 175.5 Hz); 79.1 (d, $J$ = 25.9 Hz); 58.8 (d, $J$ = 5.7 Hz); 48.5 (d, $J$ = 27.0 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −183.8 ppm (dddd, $J$ = 44, 35, 10, 7 Hz). UV−vis $\lambda_{max}$: 282, 374, 498 nm.

The fluorine diastereomer **12b** (11.9 mg, 25.1 $\mu$mol) was converted to the imide **4** (6.0 mg, 13.1 $\mu$mol, 52% yield) by the same procedure, except that 250 $\mu$L of HMDS and 15 $\mu$L of methanol were used. **4 (19*R*):** HRMS (FAB): calculated for $C_{26}H_{22}FN_3O_4$ + Na 482.1492, observed 482.1485. FTIR (neat film): 3273 cm$^{-1}$, 1719. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.03−7.95 ppm (2H); 7.43−7.21 (9H); 4.94 (1H, dddd, $J$ = 42.9, 8.5, 3.3, 3.3 Hz); 4.55 (1H, ddd, $J$ = 14.8; 8.5, 5.7 Hz); 4.40−4.20 (2H); 4.15 (1H, ddd, $J$ = 14.5, 8.8, 1.9 Hz); 4.02 (1H, ddd, $J$ = 10.2, 8.8, 1.0 Hz); 3.83 (1H, m); 3.77 (1H, ddd, $J$ = 10.8, 4.4, 1.9 Hz); 3.75−3.64 (2H). $^{13}$C NMR {H} (151 MHz, $CDCl_3$): 90.1 ppm (d, $J$ = 176.4 Hz); 78.6 (d, $J$ = 25.3 Hz); 46.1 (d, $J$ = 33.0 Hz). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −186.8 ppm (ddddd, $J$ = 43, 15, 12, 6, 3 Hz). UV−vis $\lambda_{max}$: 290, 372, 496 nm.

**(18*R*,19*S*)- and (18*R*,19*R*)-19-Fluoro-18-[(dimethylamino)methyl]-17-oxa-4,14,21-triazahexacyclo[19.6.1.1$^{7,14}$.0.$^{2,6}$.0$^{8,13}$.0$^{22,27}$]nonacosa-1(28),2(6),7(29),8,10,12,22(27),23,25-nonaene-3,5-dione (1 and 2).** A solution of the primary alcohol **3** (31 mg, 0.067 mmol) in THF (15 mL) was treated with triethylamine (210 $\mu$L, 1.56 mmol), and methanesulfonyl chloride (85 $\mu$L, 1.02 mmol) was added. The reaction mixture was stirred at room temperature under $N_2$ for 3 h. The mixture was concentrated under reduced pressure, taken up in methylene chloride, and washed with 1 N HCl and brine. Drying over $Na_2SO_4$ and evaporation yielded the crude mesylate. A solution of the crude mesylate in THF (6 mL) was treated with dimethylamine (40% aqueous, 1 mL), and the flask was sealed with a Teflon stopper and stirred at 50 °C for 24 h. The flask was cooled to 0 °C and opened, and the volatiles were removed under reduced pressure. Silica gel chromatography in 0−10% triethylamine in ethyl acetate yields the dimethylamine **1** (13.2 mg, 0.027 mmol, 40% yield) as a purple-red solid. **1 (19*S*):** HRMS (FAB): calculated for $C_{28}H_{27}FN_4O_3$ + Na 509.1965, observed 509.1971. FTIR (neat film): 3053 cm$^{-1}$, 1715. $^1$H NMR (300 MHz, $CDCl_3$−$C_6D_6$, 2:1): $\delta$ 8.12−7.95 (2H); 7.30−7.05 (9H); 4.67 (1H, dddd, $J$ = 43.9, 7.4, 4.0, 3.2 Hz); 4.14 (1H, ddd, $J$ = 20.4, 14.9, 3.2 Hz); 4.02 (1H, ddd, $J$ = 14.9, 14.9, 7.4 Hz); 3.94 (1H, ddd, $J$ = 15.0, 4.0, 4.0 Hz); 3.81 (1H, ddd, $J$ = 150, 4.2, 5.6 Hz); 3.58 (2H, dd, $J$ = 4.2, 4.8 Hz); 3.47 (1H, dddd, $J$ = 14.0, 4.5, 4.3, 4.2 Hz); 1.79 (6H, s); 1.73 (1H, ddd, $J$ = 13.4, 4.5, 2.8 Hz); 1.64 (1H, dd, $J$ = 13.4, 4.3 Hz). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 172.7 ppm; 172.6; 137.6; 136.8; 134.1; 133.7; 128.6; 128.0; 123,0; 122.7; 122.6; 121.3; 121.1; 111.1; 110.7; 105.5; 104.6; 90.9 (d, $J$ = 175.1 Hz); 79.6 (d, $J$ = 21.3 Hz); 69.3; 59.3 (d, $J$ = 8.8 Hz); 47.7; 46.6 (d, $J$ = 31.6 Hz); 45.9. $^{19}$F NMR (376 MHz, acetone-$d_6$): $\delta$ −187.3 ppm (ddddd, $J$ = 43, 15, 15, 15, 3 Hz). UV−vis $\lambda_{max}$: 282, 372, 494 nm.

The fluorine diastereomer **4** (3.4 mg, 7.4 $\mu$mol) was converted to the dimethylamine **2** (1.9 mg, 3.9 $\mu$mol, 53% yield after recrystallization from methylene chloride−hexane) by the same procedure. **2 (19*R*):** FTIR (neat film): 3051 cm$^{-1}$, 1703. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.05−7.95 ppm (2H); 7.40−7.20 (8H); 4.86 (1H, dddd, $J$ = 43.2, 7.9, 3.2, 3.0 Hz); 4.50−4.30 (3H); 4.20−4.00 (2H); 3.80−3.60 (3H); 2.50−2.30 (2H, m); 2.09 (6H, s). $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −180.9 ppm (m). UV−vis $\lambda_{max}$: 282, 384, 498 nm.

**(2*S*,3*R*)-3-[(2*R*)-1,4-Dioxaspiro[4.5]decanyl]-2-fluoro-3-(2-hydroxypropoxy)-propan-1-ol (14).** A solution of 9-BBN (0.5 M in THF, 1.0 mL, 0.50 mmol) at 0 °C under $N_2$ was treated with a solution of **9a** (69 mg, 0.250 mmol) in THF (2 mL). The solution was stirred at room temperature for 3 h. The mixture was treated with NaOH (3 N, 1 mL) and 30% $H_2O_2$ (2 mL). The solution was adjusted to pH 8 and stirred at 50 °C for 1 h.[28] The reaction was cooled to room temperature, diluted with ethyl acetate, and washed with saturated $K_2CO_3$, water, and brine. The organic layer was dried over $Na_2SO_4$ and evaporated at reduced pressure. The residue was chromatographed on silica gel column using 1:1 ethyl acetate−hexane and then ethyl acetate as eluent, yielding the diol **14** (48 mg, 0.164 mmol, 66% yield) as a clear colorless oil, along with recovered starting material (13 mg, 19%). HRMS (EI): calculated for $C_{14}H_{25}FO_5$ 292.1686, observed 292.1685. FTIR (neat film): 3450 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.67 ppm (1H, dddd, $J$ = 47.2, 5.0, 4.1, 3.6 Hz); 4.18 (1H, ddd, $J$ = 6.1, 6.1, 6.0 Hz); 4.07 (1H, ddd, $J$ = 7.1, 7.1, 1.0 Hz); 4.00−3.65 (8H); 2.88 (1H, br. s); 2.45 (1H, br. s); 1.80 (2H, tt, $J$ = 6.0, 6.0 Hz). $^{13}$C NMR {H} (75 MHz, $CDCl_3$): $\delta$ 93.4 ppm (d, $J$ = 173.8 Hz); 79.3 (d, $J$ = 20.7 Hz); 74.2 (d, $J$ = 6.6 Hz); 70.2; 65.7; 61.6 (d, $J$ = 21.9 Hz); 60.1. $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −197.6 ppm (dddd, $J$ = 47.3, 24.5, 24.5, 14.5 Hz). $[\alpha]^{25}_D$ + 4.1° ($c$ 0.93 $CHCl_3$).

**(19*R*,20*S*)-19-[(2*R*)-1,4-Dioxaspiro[4.5]decanyl]-20-fluoro-4-methyl-18-oxa-4,14,21-triazahexacyclo[20.6.1.1$^{7,14}$.0.$^{2,6}$.0$^{8,13}$.0$^{22,28}$]triaconta-1(29),2(6),7(30),8,10,12,23(28),24,26-nonaene-3,5-dione (15).** A solution of the diol

(28) Brown, H. C.; Knights, E. F.; Scouten, G. *J. Am. Chem. Soc.* **1974**, *96*, 7765.

**14** (130 mg, 0.445 mmol) in diethyl ether (12 mL) was treated with triethylamine (600 μL, 4.2 mmol) and methanesulfonyl chloride (350 μL, 4.2 mmol). The mixture was stirred at room temperature under $N_2$ for 19 h. The reaction was quenched with water (50 mL) and stirred for 1.5 h. The reaction was diluted with ethyl acetate and washed with $NH_4Cl$, $NaHCO_3$, and brine. After drying over anhydrous $Na_2SO_4$, the solution was concentrated at reduced pressure to yield the crude dimesylate as a yellowish oil (197 mg).

To a suspension of cesium carbonate (640 mg, 1.9 mmol) in DMF (10 mL) at 50 °C under $N_2$ was added a solution of the crude dimesylate (197 mg) and 2,3-bis[1*H*-indol-3-yl]-*N*-methylmaleimide (150 mg, 0.44 mmol) in DMF (10 mL) via syringe pump over a period of 50 h. The reaction mixture was diluted with ethyl acetate and washed with water, $NaHCO_3$, and brine. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using 5% acetone−$CHCl_3$ as eluent to yield **15** as an orange-red solid (125 mg, 0.209 mmol, 47% yield). HRMS (FAB): calculated for $C_{35}H_{36}FN_3O_5$ + Na 620.2537, observed 620.2552. FTIR (neat film): 1699 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.00 ppm (1H, d, $J$ = 6.6 Hz); 7.81 (1H, d, $J$ = 7.8 Hz); 7.40 (1H, d, $J$ = 8.1 Hz); 7.34 (1H, s); 7.32−7.17 (7H); 4.93 (1H, dddd, $J$ = 44.4, 7.3, 3.7, 3.4 Hz); 4.50 (1H, ddd, $J$ = 19.6, 14.9, 3.7 Hz); 4.41 (1H, ddd, $J$ = 14.9, 9.3, 7.3 Hz); 4.16 (1H, ddd, $J$ = 14.4, 5.3, 4.4 Hz); 4.05 (1H, ddd, $J$ = 14.4, 8.3, 4.3 Hz); 3.81 (1H, dd, $J$ = 7.1, 6.2 Hz); 3.74 (1H, ddd, $J$ = 6.2, 6.1, 5.7 Hz); 3.64 (1H, dd, $J$ = 7.1, 5.7 Hz); 3.44 (1H, ddd, $J$ = 15.5, 6.3, 3.4 Hz); 3.39 (1H, ddd, $J$ = 10.5, 5.3, 5.2 Hz); 3.22 (3H, s); 3.20 (1H, m); 2.05−1.90 (2H, m). $^{13}C$ NMR {H} (150 MHz, DMSO-$d_6$): δ 171.6; 171.5; 136.9; 135.9; 133.1; 131.2; 130.2; 129.7; 126.9; 123.0; 122.6; 122.3; 121.7; 121.0; 110.1; 109.8; 109.5; 106.2; 104.6; 91.5 (d, $J$ = 179.0 Hz); 81.6 (d, $J$ = 19.9 Hz); 73.4 (d, $J$ = 8.0 Hz); 69.6; 66.4; 46.7 (d, $J$ = 30.0 Hz); 42.8; 36.2; 34.1; 29.2; 25.0; 24.1; 24.0; 23.6. $^{19}F$ NMR (376 MHz, $CDCl_3$): δ − 189.9 ppm (dddd, $J$ = 44.4, 20.2, 15.0, 9.3 Hz). $[\alpha]^{25}_D$ +9° (c 0.08 $CHCl_3$). UV−vis $\lambda_{max}$: 280, 386, 464 nm.

**(19*R*,20*S*)-20-Fluoro-19-(hydroxymethyl)-4-methyl-18-oxa-4,14,21-triazahexacyclo[20.6.1.1$^{7,14}$.0.$^{2,6}$.0$^{8,13}$.0$^{22,28}$]-triaconta-1(29),2(6),7(30),8,10,12,23(28),24,26-nonaene-3,5-dione (16).** A solution of the cyclohexylidene **15** (74 mg, 0.124 mmol) in methanol (20 mL) was treated with toluenesulfonic acid (528 mg), and the mixture was stirred at 70 °C for 5 h. The mixture was concentrated, diluted with ethyl acetate, and washed with $NaHCO_3$, water, and brine. Drying over $Na_2SO_4$ and silica gel chromatography in methylene chloride and then ethyl acetate yielded the diol and recovered starting material. The starting material was resubmitted to the same conditions to yield additional diol (51 mg).

A solution of the above diol in acetone−acetic acid (1:1, 16 mL) was treated with sodium periodate (100 mg, 0.37 mmol) in water (2 mL), and the mixture was stirred at room temperature for 2.5 h. The mixture was diluted with ethyl acetate and washed with water, $NaHCO_3$, and brine. The organic layer was dried over $Na_2SO_4$ and concentrated to yield the crude aldehyde.

A solution of the crude aldehyde in methylene chloride (7 mL) at −78 °C was treated with a fresh suspension of $NaBH_4$ (22 mg, 0.58 mmol) in ethanol (3 mL). The mixture was stirred at −78 °C under $N_2$ for 50 min. The reaction was quenched with acetaldehyde (500 μL) and warmed to room temperature. The reaction was diluted with ethanol (5 mL), treated with saturated sodium potassium tartrate, and stirred at room temperature overnight. The mixture was diluted with ethyl acetate and washed with water and brine. The product was dried over $Na_2SO_4$ and concentrated. Silica gel chromatography in 0−50% ethyl acetate−methylene chloride yields the primary alcohol **16** as an orange-red solid (46 mg, 0.090 mmol, 73% yield). HRMS (FAB): calculated for $C_{28}H_{24}FN_3O_4$ + Na 510.1805, observed 510.1799. FTIR (neat film): 3515 $cm^{-1}$, 1699. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.92−7.85 ppm (2H); 7.41 (1H, d, $J$ = 8.1 Hz); 7.38 (1H, s); 7.34 (1H, s); 7.30−7.16 (5H); 4.87 (1H, dddd, $J$ = 44.7, 6.3, 6.3, 3.2 Hz); 4.52−4.37 (2H, m); 4.17 (2H, *t*, $J$ = 6.0 Hz); 3.55 (1H, ddd, $J$ = 10.1, 3.0, 2.7 Hz); 3.49 (1H, ddd, $J$ = 10.1, 6.0, 5.5 Hz); 3.33 (1H, ddd, $J$ = 11.8, 3.4, 2.2 Hz); 3.22 (1H, m); 3.21 (3H, s); 3.06 (1H, ddd, $J$ = 10.0, 6.8, 6.8 Hz); 2.25−2.07 (2H, m); 1.65−1.50 (8H, m); 1.30−1.20 (2H, m). $^{13}C$ NMR {H} (150 MHz, $CDCl_3$): δ 110.1 (d, $J$ = 3.3 Hz); 90.4 (d, $J$ = 177.2 Hz); 80.9 (d, $J$ = 24.9 Hz); 60.2 (d, $J$ = 6.3 Hz); 48.2 (d, $J$ = 29.5 Hz). $^{19}F$ NMR (376 MHz, $CDCl_3$): δ −187.0 ppm (dddd, $J$ = 44.7, 21.7, 11.8, 11.3 Hz). UV−vis $\lambda_{max}$: 286, 388, 456 nm.

**(19*R*,20*S*)-20-Fluoro-19-(hydroxymethyl)-18-oxa-4,14,21-triazahexacyclo[20.6.1.1$^{7,14}$.0.$^{2,6}$.0$^{8,13}$.0$^{22,28}$]triaconta-1(29),2(6),7(30),8,10,12,23(28),24,26-nonaene-3,5-dione (5).** A solution of **16** (28 mg, 0.0575 mmol) in ethanol (5 mL) and 5 N KOH (5 mL) was stirred at 70 °C for 16 h. The solution was cooled to 0 °C and acidified with 5 N HCl. After 10 min of stirring, the mixture was extracted with ethyl acetate and washed with water and brine. The organic layer was dried over $Na_2SO_4$ and concentrated to yield the crude anhydride as an orange-red solid.

The crude anhydride in DMF (2 mL) was treated with hexamethyldisilazane (500 μL, 2.36 mmol) and $CH_3OH$ (48 μL, 0.62 mmol). The resulting mixture was stirred at room temperature under $N_2$ for 42 h. The mixture was diluted with $CH_3CN$−1 N HCl (2:1, 6 mL) and stirred at room temperature for 1 h. The mixture was extracted with ethyl acetate and washed with water and brine. The residue was dried over $Na_2SO_4$, concentrated, and separated on a silica gel column eluted with 0−20% $CH_3CN$ in $CH_2Cl_2$ to yield the imide **5** as a red-orange solid (18 mg, 0.038 mmol, 66% yield). HRMS (FAB): calculated for $C_{28}H_{24}FN_3O_4$ 473.1751, observed 473.1755. FTIR (neat film): 3258 $cm^{-1}$, 1719. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.87 ppm (2H, d, $J$ = 7.4 Hz); 7.74 (1H, s); 7.38 (1H, d, $J$ = 8.1 Hz); 7.37 (1H, s); 7.33 (1H, s); 7.30−7.17 (5H); 4.83 (1H, dddd, $J$ = 44.7, 6.3, 6.3, 3.2 Hz); 4.48−4.25 (2H, m); 4.10 (2H, *t*, $J$ = 5.7 Hz); 3.55 (1H, ddd, $J$ = 10.1, 3.0, 2.7 Hz); 3.49 (1H, br. d, $J$ = 11.5 Hz); 3.46 (1H, ddd, $J$ = 10.1, 6.0, 6.0 Hz); 3.32 (1H, m); 3.20 (1H, dddd, $J$ = 10.7, 6.5, 3.7, 3.7 Hz); 3.06 (1H, ddd, $J$ = 10.1, 6.8, 6.6 Hz); 2.25−2.07 (2H, m). $^{13}C$ NMR {H} (150 MHz, $CDCl_3$): δ 110.1 ppm (d, $J$ = 3.4 Hz); 89.3 (d, $J$ = 177.0 Hz); 81.0 (d, $J$ = 25.0 Hz); 60.2 (d, $J$ = 6.3 Hz); 48.2 (d, $J$ = 29.7 Hz); 42.7; 29.6. $^{19}F$ NMR (376 MHz, $CDCl_3$): δ −186.9 ppm (dddd, $J$ = 44.7, 20.7, 10.7, 10.4 Hz). UV−vis $\lambda_{max}$: 284, 394, 456 nm.

**(19*R*,20*S*)-19-[(Dimethylamino)methyl]-20-fluoro-18-oxa-4,14,21-triazahexacyclo[20.6.1.1$^{7,14}$.0.$^{2,6}$.0$^{8,13}$.0$^{22,28}$]-triaconta-1(29),2(6),7(30),8,10,12,23(28),24,26-nonaene-3,5-dione (6).** A solution of the primary alcohol **5** (17 mg, 0.036 mmol) in THF (10 mL) was treated with triethylamine (140 μL, 1.04 mmol), and methanesulfonyl chloride (56 μL, 0.67 mmol) was added. The reaction mixture was stirred at room temperature under $N_2$ for 3 h. The mixture was concentrated under reduced pressure, taken up in ethyl acetate, and washed with water and brine. Drying over $Na_2SO_4$ and evaporation yielded the crude mesylate. A solution of the crude mesylate in THF (5 mL) was treated with dimethylamine (40% aqueous, 1.5 mL), and the flask was sealed with a Teflon stopper and stirred at 50 °C for 36 h. The flask was cooled to 0 °C and opened, and the volatiles were removed under reduced pressure. Silica gel chromatography in 0−20% triethylamine in ethyl acetate yielded the dimethylamine **6**, along with recovered mesylate, which was resubmitted to the same conditions (combined yield 6.3 mg, 0.0126 mmol, 35% yield as a purple-red solid). **6:** FTIR (neat film): 3055 $cm^{-1}$, 1719. $^1H$ NMR (600 MHz, $CDCl_3$): δ 7.93 ppm (1H, d, $J$ = 7.4 Hz); 7.88 (1H, d, $J$ = 8.2 Hz); 7.44 (1H, s); 7.43 (1H, s); 7.39 (1H, d, $J$ = 8.2 Hz); 7.35 (1H, s); 7.31 (1H, d, $J$ = 8.2 Hz); 7.30−7.25 (2H); 7.21 (1H, dd, $J$ = 8.2, 8.2 Hz); 7.20 (1H, ddd, $J$ = 8.2, 7.4 Hz); 5.01 (1H, dddd, $J$ = 44.7, 8.3, 4.7, 3.7 Hz); 4.48−4.35 (2H, m); 4.28 (1H, dt, $J$ = 14.9, 6.0 Hz); 4.15 (1H, dt, $J$ = 14.9, 6.0 Hz); 3.51 (1H, dt, $J$ = 10.3, 6.0 Hz); 3.33 (1H, dddd, $J$ = 17.1, 6.7, 6.0, 3.7 Hz); 3.29 (1H, dt, $J$ = 10.3, 6.0 Hz); 2.11 (2H, dddd, $J$ = 6.0, 6.0, 6.0, 6.0 Hz); 1.96 (6H, s); 1.94 (1H, ddd, $J$ = 13.4, 6.0, 3.0 Hz); 1.81 (1H, dd, $J$ = 13.4, 6.7 Hz). $^{13}C$ NMR {H} (150 MHz, $CDCl_3$): δ 90.5 ppm (d, $J$ = 177.0 Hz); 79.1 (d, $J$ = 22.4 Hz); 69.7; 59.1 (d, $J$ = 7.1 Hz); 46.9 (d, $J$ = 21.5 Hz); 46.0;

43.6; 34.1, 29.6. $^{19}$F NMR (376 MHz, $CDCl_3$): $\delta$ −187.6 ppm (m). UV−vis $\lambda_{max}$: 284, 396, 444 nm.

**Acknowledgment.** Funding from NSF-EPSCoR (EPS-9452857), NIGMS GM55993, and the Mississippi State University Research Initiation Program are gratefully acknowledged. NMR measurements were made at the Mississippi Magnetic Resonance Facility at Mississippi State University, supported by the National Science Foundation (CHE-9214521) and Mississippi State University. Mass spectra were taken at the Harvard University Mass Spectrometry Laboratory. Helpful discussions with Dr. Ad Bax and Dr. Peter Morken are gratefully acknowledged.

**Supporting Information Available:** Copies of $^1$H NMR spectra and characterization data (high- and low-resolution mass, FTIR, proton NMR, carbon NMR, fluorine NMR, $[\alpha]_D$, and UV−vis) for all intermediates, $^1$H NMR spectra of **8a**·(+)-Eu(tfc)$_3$ and **8a**·(−)-Eu(tfc)$_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9808876