Total Synthesis of (+)-10,10-Difluorothromboxane A_2 and Its 9,11 and 15 Stereoisomers

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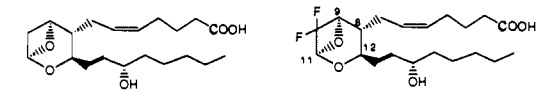
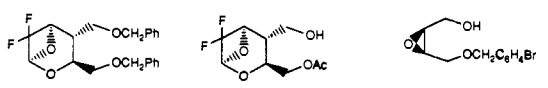
Abstract: An efficient total synthesis of the biologically highly active, stable (+)-10,10-difluorothromboxane A_2, possessing the absolute configuration of TXA_2, from the chiral synthon (−)-**5** is described. The key intermediate, the aldehyde **25**, is prepared in 16 steps with a total yield of 8.8%, which compares with 1.95% in 14 steps by our previously reported chemical–enzymatic route. Diastereoselectivity is high in all but one of the steps, the Reformatsky reaction, which leads to **13** and **14**. However, both epimers have been converted efficiently to **25**. The synthesis of the 9β,11β diastereomer **46** is also described. As predicted, the geometrically equivalent isomer showed significant binding to the platelet receptor at K_d = 240 nM. It is, however, only a weak agonist causing aggregation of washed human platelets at 0.7% of the activity of **2**. These data are rationalized in terms of an obligatory hydrogen bond between the 9α,11α-oxetane oxygen of **2** and its receptor to achieve full biological activity.

Introduction

Thromboxane A_2 (TXA_2), the powerful vasoconstricting and platelet-aggregating substance produced enzymatically from arachidonic acid via the cyclooxygenase pathway,[1] has received much attention because of its central role in a number of pathological states such as angina, myocardial infarction, asthma, and hepatorenal disease.[2-6] It is unique among eicosanoids because of its oxetane structure, which suffers facile hydrolytic cleavage even at pH 7.4 ($t_{1/2}$ = 30 s) by a general-acid-catalyzed reaction.[7] Its chemical synthesis has only recently been described.[8] As a result, there has been much interest in synthesizing stable analogues of this important substance in order to mimic its biological properties, inhibit its biosynthesis, or serve as receptor antagonists.[9] It is a common feature of these reports that stabilization of the molecule is achieved by replacement of one or both of the acetalic oxygens by carbon or sulfur.

In recent communications[10,11] from this laboratory, we reported on the synthesis of 10,10-difluorothromboxane **2**, F_2TXA_2, its remarkable stability toward hydrolytic cleavage, its powerful contractile effects on vascular tissues and its ability to initiate platelet aggregation. A detailed account of these biological effects has also been published.[12]





The prediction that substitution of fluorine for hydrogen α to the acetalic linkage could increase the acid stability of the latter was borne out beyond our expectations. The second-order rate constant of hydrolysis of the model substance **3** was found to be 2.4×10^{-3} M^{-1} s^{-1} at 23 °C, which compares with $k = 5.5 \times 10^5$ M^{-1} s^{-1} for TXA_2 at 37 °C, a 10^8-fold *decrease* in rate. The magnitude of this rate deceleration is indeed impressive when one considers that the rate of hydrolysis of diethyl acetal is about 100 times faster than that of **3**. This finding justified the conclusion that F_2TXA_2 would be stable under conditions of biological experimentation. It also permitted the design of a synthesis in which the 7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane nucleus could be constructed first and all operations involving the side chains could be performed at a later stage. Such a strategy is of extreme importance since it permits the tying up of three functional groups in an internally protected structure, thereby avoiding the complex manipulations of protecting groups. In our earlier communication,[11] the point of departure was the diacetate prepared from the racemic dibenzyl ether **3**,[10] which in a regio- and enantiospecific reaction with pig liver esterase (PLE) was converted in 50% yield to the (+)-monoacetate **4** possessing the absolute configuration of TXA_2. This fortuitous result allowed the uneventful completion of the synthesis of (+)-F_2TXA_2 by conventional prostaglandin technology. This synthesis is conceptually extremely simple, utilizing only a single external protecting group to deal with the complex array of functionality hidden in the TXA_2 structure. It suffers only from the shortcoming that one-half of the material is discarded in the course of the kinetic resolution involved in the PLE reaction.

Synthesis of F_2TXA_2

In this paper we describe an all-chemical route to F_2TXA_2 starting with the crystalline, chiral synthon (−)-**5**.[13] This readily available compound offered the opportunity of avoiding the wasteful resolution sequence, while at the same time preserving the basic strategy employed in our earlier work.[10,11] This strategy is best discussed with the aid of retrosynthetic analysis, shown in structures **6–9**. It will be readily conceded that **6** can be

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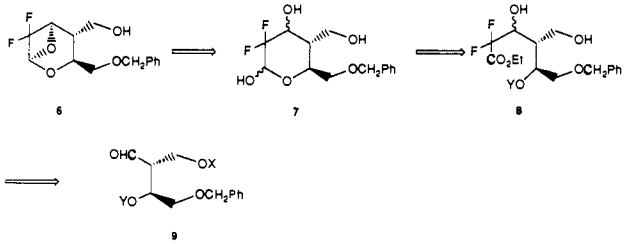


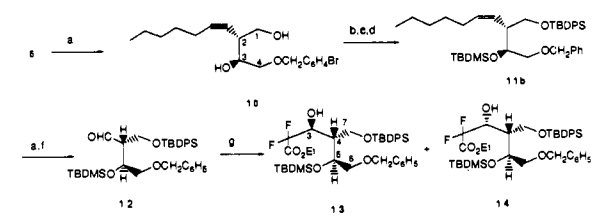
converted to **2**, following the procedure described by us for (+)-**4**.[11] It is also apparent that this scheme permits the synthesis of bicyclic oxetanes of type **33** and therefore of F_2TXA_2 isomers such as **46**, in which the two bridgehead stereogenic centers at C-1 and C-3 (C-9 and C-11 in TXA_2 nomenclature) are of opposite chirality. Such structures were of considerable interest to us for the following reasons. Differing only by exchange of the oxetane oxygen for the CF_2 group, they show close geometric similarity to that of F_2TXA_2, a change which would not be expected to interfere with binding to the TXA_2 receptor. On the other hand, nonbonding and hydrogen-bonding interaction with the receptor could be significantly altered with serious consequences for biological activity. As will be pointed out later, both expectations were borne out experimentally.

While the starting material in our earlier synthesis was the symmetrical 1,4-bis(benzyloxy)-2,3-oxidobutane, our present starting material is the disymmetric **5**[13] (Scheme I). This causes a number of problems, not the least of which are associated with the requirement for additional protecting groups in a system where every carbon except C-1 is functionalized. More serious at this stage was the fact that a regiospecific opening of the epoxide **5** leading to a 1,3-diol aldehyde such as **9** had to be devised. Our solution was based on earlier work from this laboratory involving the regiospecific opening of hydroxyl-substituted epoxides with dimethylalkynylalanes.[14,15] The resulting acetylenic alcohol would then be converted to the desired aldehyde **9**, by partial reduction to the olefin followed by ozonolysis.

Reaction of epoxide **5** with dimethylheptynylalane did not show the required regioselectivity, affording instead a mixture of the acetylenic 1,3-diol **10** and significant amounts of the isomeric 1,2-diol, as demonstrated by oxidation with lead tetraacetate. It has recently been shown that the use of dimethyldialkynylalanates can substantially increase the regioselectivity in epoxide opening reactions.[16] This modification, when applied to **5**, resulted in a 19:1 mixture of the desired acetylenic 1,3-diol (**10**) and the isomeric 1,2-diol, which on crystallization from ether/petroleum ether furnished pure **10** in 74.5% yield. Catalytic reduction with 5% $Pd/BaSO_4$ in pyridine gave the cis olefin **11**, with simultaneous loss of bromine, in 92% yield. Prior to conversion of **11** to the required aldehyde **9** (**12**), the two free hydroxyl groups of **10** had to be protected in such a manner as to permit the introduction and removal of the respective groups in a selective manner. We chose the diphenyl-*tert*-butylsilyl group for the protection of the primary hydroxyl group, which by the excellent method of McDougal et al.[17] gave exclusively the monoether **11a**.[18] The TBDMS ether **11b** was prepared in 85% yield from **11a**.[19,20]

Ozonolysis of the disilyl ether **11b** proceeded in excellent yield (84%), but only when the reaction was carried out in methylene chloride in the presence of 1.5 equiv of methanol. These conditions were determined after it was realized that ozonolysis in either pure CH_2Cl_2 or CH_2Cl_2/CH_3OH (1:1) yielded no more than 50% of the aldehyde **12**, together with varying amounts of a less polar

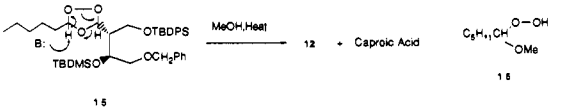
Scheme I[a]



[a] Conditions: (a) $Me_2(C_7H_{11})_2AlLi$, toluene, 23 °C; (b) $Pd/BaSO_4$, py; (c) NaH, TBDPSCl, 23 °C; (d) TBDMSCl, TEA, DMAP; (e) O_3; (f) Me_2S; (g) $BrCF_2CO_2Et$, Zn, THF, 22 °C.

side product which gave analytical figures and spectral data, as well as all of the reactions expected of ozonide **15** as a mixture of diastereomers. Thus, treatment of **15** with pyridine, methanol, dimethyl sulfoxide, or hydrogen and Pd/C produced the aldehyde **12** in quantitative yield. The fragmentation of ozonides initiated by these reagents is well documented.[21] Particularly convincing was the reaction with hot methanol carried out in an NMR tube, which resulted in the spectrum of an equimolar mixture of **12** and caproic acid, with deprotonation occurring at the less sterically hindered side of the ozonide.

There are two surprising aspects to the isolation of the ozonide **15** under the standard conditions for ozonolysis. One is the unusual resistance of **15** to reduction by dimethyl sulfide which, however, is not unprecedented.[22] The second is the fact that, while excess methanol leads to the formation of the ozonide **15**, a stoichiometric amount does not. In the latter case, the reaction with ozone must involve intermediates other than the stable ozonide and lead instead to the aldehyde **12** and the α-methoxy hydroperoxide **16**, which later is reduced by dimethyl sulfide. The hydroperoxide **16** arises from the carbonyl oxide, which rather than recombining with the hindered aldehyde is trapped by methanol to form **16**.[23] While the isolation of the ozonide **15** with methylene chloride as the solvent would be expected, its formation in 1:1 CH_2Cl_2/CH_3OH is not readily apparent. A possible explanation is the high polarity of this solvent mixture, which favors the dipolar addition of the carbonyl oxide to the aldehyde over reaction with methanol.



For the introduction of the required fluorine and oxygen functionalities, we employed the Reformatsky reaction with ethyl bromodifluoroacetate, introduced by us[10,11,24] for this purpose and since employed widely by others[25] (Scheme I). Attempts to use the less expensive ethyl chlorodifluoroacetate in DMF[26] led only to the recovery of unchanged starting material. The yield of the isomeric hydroxy esters **13** and **14** has been substantially improved to 81% by conducting the reaction at room temperature with initial cooling. Under these conditions, the isomer ratio of **13**:**14** was 1.38:1.

The stereochemistry of the newly introduced hydroxyl group in the two isomers was deduced unambiguously from the proton and fluorine NMR spectra of the lactol mesylates **19** and **28** obtained further along in the synthesis and derived from **14** and **13**, respectively. Because of the importance of this assignment for the ensuing discussion, it will be dealt with at this point. The lactol mesylates **19** and **28** appeared to be ideally suited for this purpose. Because of the two large trans-oriented 4-(silyloxy) and

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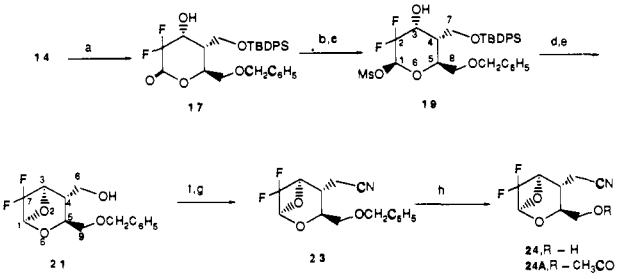
Scheme II[a]



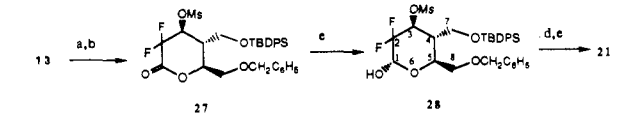
[a] Conditions: (a) $AcOH/H_2O$, 65 °C; (b) $NaBH_4$; (c) MsCl, py; (d) K_2CO_3; (e) Bu_4NF; (f) TsCl, py; (g) NaCN, DMF; (h) Pd/C, Me_2CHOH.

5-(benzyloxy) substituents, the tetrahydropyran ring was expected to show preference for a single chair conformation, permitting NMR coupling constants between neighboring protons and fluorines to be interpreted safely in terms of relative stereochemistry. The spectrum of the 3β-mesylate **28** proved particularly instructive in that it shows H-3 as an 8-line signal at δ 5.61 with diaxial coupling to fluorine (J = 20.2 Hz) and to H-4 (J = 11.4 Hz). The signal for H-4 at δ 2.22, in turn, appears as a broad triplet with J = 10–11 Hz, indicating diaxial coupling with H-5 as well. The signal for H-5 is obscured by overlap with one of the methylene signals for the benzyl group. These assignments are confirmed by double irradiation experiments, which also serve to provide the assignments for the H-7 and H-8 methylene protons, with H-8 absorbing upfield from H-7. The spectrum for the 3α-ol 1β-mesylate **19** is less definitive since the H-3 signal overlaps with one of the benzyl proton signals. It is however possible to conclude that H-3 must be equatorial and therefore β-oriented, since its coupling to F_β is very small, too small to be measured. F_β is clearly identified by its single measurable $J_{H,F}$ = 15.3 Hz, indicating diaxial coupling to H-1α (δ = 5.82, J = 15.3 Hz) which establishes the configuration of the mesyloxy group as 1β.

As the stereochemistry at C-3 of the Reformatsky esters **13** and **14** has been secured, only simple functionality changes remain prior to completing the bicyclic oxetane acetal structure. It is an important feature of this synthesis that both epimers can be utilized for the conversion to the important oxetane acetal **21** and thus to the target compounds. Starting with **14** (Scheme II), the required lactol mesylate **19** was obtained by partial desilylation–lactonization with 90% acetic acid/H_2O, followed by borohydride reduction and mesylation, with the three steps giving near quantitative yields. The lactol intermediate **18** is a mixture of anomers which is readily equilibrated by treatment with base. Thus, when **18** is treated with mesyl chloride and pyridine, a single 1β-mesylate **19** is formed, so formulated because of the large diaxial coupling constants for H-1 ($J_{H,F}$ = 15.4 Hz), leaving the 3α-hydroxyl group unsubstituted. This is a most fortunate event since the C-1 and C-3 functionalities are appropriately set up for oxetane formation by nucleophilic attack of the 3-oxy anion at C-1. Indeed, cyclization occurred in 77% yield under remarkably mild conditions: treatment with 0.05 M potassium carbonate in 80% aqueous methanol for 15 h. These conditions are noteworthy in another respect as well. While in our earlier work[10] cyclizations to form 1,3-oxetanes were performed with strict exclusion of nucleophilic solvents to avoid attack by solvent, we were astonished to find no evidence at all for such side reactions. Moreover, the yields under these conditions were superior to any others tried.

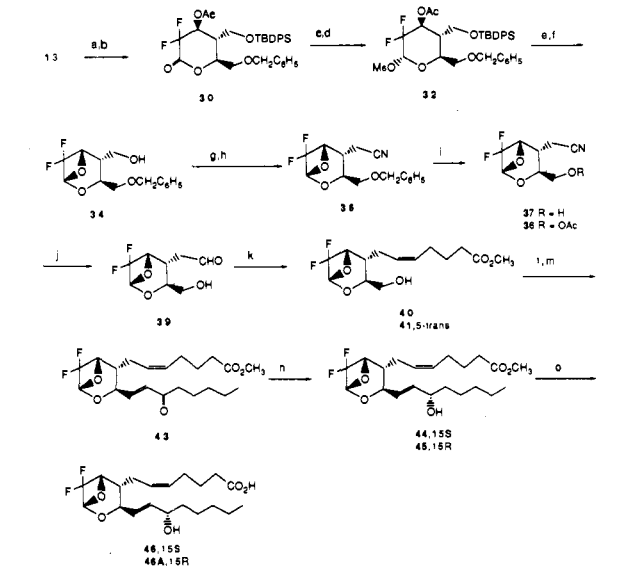
The conversion of the 3β epimer **13** of the Reformatsky product to the oxetane requires some minor modifications of the above reaction sequence. In this case (Scheme III), it was necessary to convert the 3β-hydroxyl group into a leaving group. Since acylation of the lactol at C-1 was expected to be preferred, **13** was first converted to the 3β-mesylate **26** followed by lactonization to **27**. With this slight change the lactol 3β-mesylate **28** was prepared in 75% yield from **13** as a mixture of anomers. Applying the dilute carbonate cyclization procedure to this mixture led only to equilibration resulting in the formation of the pure α anomer.

Scheme III[a]



[a] Conditions: (a) MsCl, py; (b) $AcOH/H_2O$, 65 °C; (c) $NaBH_4$; (d) $LiN(TMS)_2$, HMPA, 60 °C; (e) Bu_4NF.

Scheme IV[a]



[a] Conditions: (a) $AcOH/H_2O$, 65 °C; (b) Ac_2O, py; (c) $NaBH_4$; (d) MsCl, py; (e) K_2CO_3, MeOH; (f) Bu_4NF; (g) TsCl, py; (h) NaCN, DMF; (i) Pd/C, Me_2CHOH; (j) DIBAL-H; (k) $BrPh_3P(CH_2)_4CO_2H$, $LiN(TMS)_2$; (l) $(COCl)_2$, DMSO; (m) $(Me_3O)_2POCH_2CO(CH_2)_4CH_3$, $LiN(TMS)_2$; (n) $NaBH_4$, $CeCl_3$; (o) NaOH.

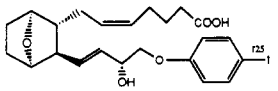
Cyclization to the oxetane **20** required treatment with lithium hexamethyldisilazide in DMF/HMPA at 60 °C. These strongly basic conditions caused some loss of the silyl ether. The resulting mixture was therefore converted directly to the alcohol **21** with tetrabutylammonium fluoride in 80% yield from **28**.

At this point, the major objective, the construction of the bicyclic ring system of difluorothromboxane A_2 with two differentially protected appendages for elaborating the side chains, had been achieved. To complete the synthesis (Scheme II), the benzyl ether **21** is converted into the nitrile **23** via the tosylate **22**, to be followed by debenzylation to **24** in 52% yield for the three steps from **21**. At this stage, the synthesis links up with our alternative procedure involving the regio- and enantioselective deacylation of the diacetate prepared from (±)-**3** with pig liver esterase reported earlier.[11]

Synthesis and Biological Properties of 9β,11β-Oxido-10,10-Diflorothromboxane A_2

For the synthesis of the 9β,11β isomer of F_2TXA_2, **46**, and its 15*R* isomer, **46A** (Scheme IV), we have arbitrarily chosen to start with the 3β Reformatsky ester **13**, although the chemistry described in the foregoing would be applicable to the 3α isomer, **14**, as well. In this case, introduction of the β-oxido bridge required a free hydroxyl group at C-3 and a leaving group in the 1α position. The ester **13** was therefore cyclized to the lactone **29**, and the 3β-hydroxyl group was protected by acetylation (**30**). Borohydride reduction yielded exclusively the 1α anomer **31** ($J_{H,F}$ = 5.3 Hz), which was converted to the desired 1α-mesylate **32** ($J_{H,F}$ = 4.5 Hz). As in the case of the 3α-hydroxy-1β-mesylate **19**, cyclization occurred readily, after deacetylation, with 0.05 M K_2CO_3 in 80% methanol/water to form the oxetane **33** (10% desilylated), which was isolated after complete desilylation to **34**. The yield in the six steps from **13** was 29%. The completion of the synthesis follows classical prostaglandin methodology and is described in the Experimental Section.

The ability of **46** and **46A** to compete for the platelet receptor with the ^{125}I-labeled TXA_2/PGH_2 receptor agonist **47**[27] was measured using washed human platelets. The *S* isomer **46** bound to the receptor with a K_d of 240 nM, while the unnatural *R* isomer had a K_d of 1.43 μM. This compares with K_d = 100 and 280 nM for $DFTXA_2$ and its 15*R* isomer, respectively. Compound **46** caused no aggregation of washed human platelets at 1 μM, a concentration at which $DFTXA_2$ produced a maximal response (EC_{50} = 36 nM). At 5 and 10 μM, compound **46** showed weak, concentration-dependent aggregation and at these concentrations acted as an antagonist toward **47**, a characteristic of partial agonists.



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The above data clearly demonstrate that the geometrically equivalent stereoisomers **2** and **46** show only minor differences in binding to the platelet receptor. On the other hand, exchange of the oxido and CF_2 groups causes a substantial drop in biological activity. These findings support the view that a hydrogen-bonding interaction between the 9α,11α-oxido bridge and the receptor may be essential for producing the conformational change in the receptor required for a maximal biological response.

Conclusion

The efficiency of the synthetic routes described in this paper may be gauged from the results obtained for the important aldehydic intermediate **25**. This compound is obtained from the chiral synthon (−)-**5** in 8.8% yield in 16 steps, many of them without further purification of intermediates, although all intermediates were characterized after isolation in pure form. This compares with 1.95% in 14 steps by the combined chemical–enzymatic route.[11] Most of the gains in yield are the result of the use of the chiral starting material and the applicability of the synthesis to both epimers from the Reformatsky reaction.

Experimental Section

Methods and Instrumentation. Thin-layer chromatograms were run on 1.25-mm EM precoated plates of silica gel 60 F254. Compounds were visualized with 10% phosphomolybdic acid in ethanol using heat to develop the plates. The routine workup of the organic phase, after the appropriate washes, consisted of drying over anhydrous sodium sulfate, filtration, removal of the solvent at room temperature under house vacuum or under a stream of nitrogen, and purification of the product by column chromatography according to Still et al.[28] Melting points were obtained on a Thomas-Hoover melting point apparatus and were not corrected. The ^{1}H NMR spectra were obtained in $CDCl_3$ on a University of Chicago DS-1000 spectrometer at 500 MHz and were processed by Fourier transformation using a Nicolet Instrument Corporation 1180 or 1280 data acquisition system. The ^{19}F NMR spectra were obtained on a Varian XL-400 instrument at 376.2 MHz (in $CDCl_3$) with the use of a 1280 data acquisition system. The chemical shifts of the ^{1}H NMR signals are reported in δ parts per million (ppm) with chloroform as internal standard (δ 7.25). The chemical shifts of the ^{19}F NMR signals are reported in ϕ ppm upfield from the internal standard $CFCl_3$. Coupling constants, *J*, are reported in hertz. The abbreviations s, d, t, q, p, m, and br signify singlet, doublet, triplet, quartet, quintet, multiplet, and broad, respectively. High-resolution mass spectra were determined at 50 eV on a VG 70-250 E mass spectrometer equipped with GLC gas and solid probe inlets. HPLC separations and purifications were performed using a Waters Associates RCM-100 radial compression module in conjunction with a Waters Associates Model 590 programmable solvent delivery module, a UGK injector, and a 0.2-μm prefilter. Elemental analyses were performed by Midwest Microlab, Indianapolis, IN.

(2*S*,3*R*)-1-Hydroxy-4-[(*p*-bromobenzyl)oxy]-2,3-oxidobutane (5).[13] To a cold (−20 °C) suspension of powdered 4-Å molecular sieves (24.8 g) in dry CH_2Cl_2 (1600 mL) under nitrogen atmosphere was added titanium tetraisopropoxide (18.16 g, 64 mmol), L-(+)-diisopropyl tartrate (20.48 g, 88 mmol), and *tert*-butyl hydroperoxide (176.8 mL of 3.615 M solution in toluene). The slurry was stirred at −20 °C for 30 min, and crude (*Z*)-4-[(*p*-bromobenzyl)oxy]-2-buten-1-ol (82.7 g, 0.32 mol)[13] in 50 mL of CH_2Cl_2 was added. The reaction mixture was stirred at −20 °C for 2 h and then stored in a −20 °C freezer for 2 days, following which the reaction mixture was vigorously stirred and quenched with water (400 mL). After the mixture was warmed to room temperature and stirred for 60 min, a solution of 30% NaOH in brine (10.0 mL) was added. After 30 min of vigorous stirring, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were dried ($MgSO_4$) and filtered through a pad of Celite. After evaporation of solvent, 62.2 g of crude product was obtained (80% yield): mp 40–45 °C, $[\alpha]^{20}_D$ = −16.2° ($CHCl_3$, *c* = 1.65). The crude epoxide was crystallized twice from petroleum ether/ether to yield 51.0 g of pure epoxide **5**: mp 49–50.5 °C; $[\alpha]^{20}_D$ = −17.74° ($CHCl_3$, *c* = 1.49), reported[13] −17.3°; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 and 7.2 (AB q, 4 H, phenyl, J_{AB} = 8.0 Hz), 4.57 and 4.50 (AB q, 2 H, CH_2-benzyl, J_{gem} = 12.0 Hz), 3.77 (d, 2 H, H-1, *J* = 5.0 Hz), 3.70 (m, 2 H, H-4), 3.30 (q, 1 H, H-3, *J* = 5.0 Hz), 3.25 (q, 1 H, H-2, *J* = 5.0 Hz).

(2*R*,3*S*)-1,3-Dihydroxy-2-(1-hexynyl)-4-[(*p*-bromobenzyl)oxy]butane (10). To a solution of 1-heptyne (113.5 mL, 0.865 mol) in 100 mL of toluene at 0 °C was added a solution of *n*-BuLi (182.3 mL of a 2.5 M solution in hexane, 0.456 mol) dropwise. The mixture was stirred for 15 min, and then 228.0 mL of dimethylchloroalane (1.0 M solution in hexane, 0.228 mol) was added dropwise. Stirring was continued at 0 °C for 50 min, following which a solution of epoxy alcohol **5** (31.1 g, 0.114 mol) in 150 mL of toluene was added. The cooling bath was removed, and the mixture was stirred at room temperature for 24 h. After the mixture was cooled to 0 °C 100 mL of a saturated solution of Na_2SO_4 was added dropwise. The mixture was filtered through a pad of Celite, and the organic layers were separated. The aqueous layer was extracted with ether (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness, leaving 45.0 g of crude product. Separation of the crude mixture by flash chromatography (hexane:EtOAc = 5:2) showed the ratio of 1,3-diol to 1,2-diol to be 95:5. After two crystallizations from petroleum ether/ether, 31.3 g of pure 1,3-diol **10** was obtained (74.5% yield): mp 57.5–59.0 °C; $[\alpha]^{20}_D$ = −27.69° ($CHCl_3$, *c* = 1.56); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 and 7.20 (AB q, 4 H, phenyl, J_{AB} = 8.3 Hz), 4.54 and 4.52 (dd, 2 H, CH_2-benzyl, J_{gem} = 12.1 Hz), 3.98 (m, 1 H, H-3), 3.79 (m, 2 H, H-1), 3.61, 3.59 (dd's, 2 H, H-4, J_{gem} = 9.5 Hz, $J_{4_1,3}$ = 6.7 Hz, $J_{4_2,3}$ = 5.2 Hz), 2.85 (m, 1 H, H-2), 2.46 (d, 1 H, 3-OH, *J* = 5.3 Hz), 2.20 (dt, 2 H, H-3′, $J_{3',4'}$ = 7.0 Hz, $J_{3',2}$ = 2.1 Hz), 2.15 (t, 1 H, 1-OH, *J* = 6.3 Hz), 1.50 (p, 2 H, H-4′, *J* = 7.1 Hz), 1.35 (m, 4 H, H-5′, H-6′), 0.9 (t, 3 H, H-7′, *J* = 6.8 Hz). Anal. Calcd for $C_{18}H_{25}O_3Br$: C, 58.53; H, 6.82; Br, 21.60. Found: C, 58.73; H, 6.90; Br, 21.67.

(2*R*,3*S*)-1,3-Dihydroxy-2-(1-hexenyl)-4-(benzyloxy)butane (11). To 6.018 g (0.02 mol) of 1,3-diol **10** in 200 mL of pyridine was added 2 g of Pd/$BaSO_4$ (5%). The reaction mixture was hydrogenated at atmospheric pressure until completion (disappearance of the AB quartet at 7.46 and 7.20 in the ^{1}H NMR, ca. 20 h), and the suspension was filtered through a pad of Celite. The filtrate was evaporated to dryness, and the residue was suspended in 50 mL of ethyl acetate and filtered again through a pad of Celite. After evaporation to dryness, 4.357 g of crude **11** was obtained (92% yield): $[\alpha]^{20}_D$ = +17.19° ($CHCl_3$, *c* = 1.83); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.30 (m, 5 H, phenyl), 5.64 (dt, 1 H, H-2′, $J_{2',1'}$ = 11.0 Hz, $J_{2',3'}$ = 7.3 Hz), 5.40 (t, 1 H, H-1′, *J* = 10.6 Hz), 4.56 (s, 2 H, CH_2-benzyl), 4.05 (m, 1 H, H-3), 3.73 and 3.68 (two dd, 2 H, H-1, J_{gem} = 10.7 Hz, $J_{1_1,2}$ = 6.6 Hz, $J_{1_2,2}$ = 5.6 Hz), 3.49 (d, 2 H, H-4, *J* = 5.9 Hz), 2.76 (m, 1 H, H-2), 2.04 (m, 2 H, H-3′), 1.40–1.25 (m, 6 H, H-4′, H-5′, H-6′), 0.90 (t, 3 H, H-7′, *J* = 6.6 Hz). Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.73; H, 9.50.

(2*S*,3*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-(1-hexenyl)-3-hydroxy-4-(benzyloxy)butane (11a). Sodium hydride (585 mg, 14.6 mmol) was washed twice with dry hexane (5 mL), and 20 mL of dry THF was added. A solution of the diol **11** (4.06 g, 13.9 mmol) in 5 mL of THF was added slowly over a period of 15 min, and the reaction mixture was stirred at room temperature for 45 min. *tert*-Butyldiphenylsilyl chloride (3.62 mL, 13.9 mmol) in 5 mL of THF was then added, and the whole reaction mixture was stirred at room temperature for 90 min before it was poured onto ether (100 mL), and washed with 10% aqueous K_2CO_3 solution (30 mL) and saturated sodium chloride (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting oil was purified on a silica gel column (3.5 × 20 cm) with 5% EtOAc/hexane as eluant: yield of **11a**, 6.53 g (90%); $[\alpha]^{20}_D$ = −16.5° ($CHCl_3$, *c* = 1.37); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72–7.25 (m, 15 H, 3 phenyls), 5.53 (dt, 1 H, H-2′, $J_{2',1'}$ = 10.9 Hz, $J_{2',3'}$ = 7.2 Hz), 5.47 (t, 1 H, H-1′, *J* = 10.4 Hz), 4.55 and 4.54 (d's, 2 H, CH_2-benzyl, J_{gem} = 11.9 Hz), 4.24 (m, 1 H, H-3), 3.80 (dd, 1 H, H_{1_1}, J_{gem} = 9.9 Hz, $J_{1_1,2}$ = 7.1 Hz), 3.67 (dd, 1 H, $H\text{-}1_2$, J_{gem} = 9.9 Hz, $J_{1_2,2}$ = 4.5 Hz), 3.49 (d, 2 H, H-4, *J* = 6.0 Hz), 2.75

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(d, 1 H, OH, J = 2.6 Hz), 2.72 (m, 1 H, H-2), 1.92 (q, 2 H, H-3′, J = 7.1 Hz), 1.32–1.18 (m, 6 H, H-4′, H-5′, H-6′), 1.10 (s, 9 H, t-$C_4H_9SiPh_2$), 0.88 (t, 3 H, H-7′, J = 7.2 Hz); HRMS calcd for $C_{24}H_{31}O_3Si$ (M − tBu − Ph − H, 38) 395.2042, m/z 395.2063. Anal. Calcd for $C_{34}H_{46}O_3Si$: C, 76.93; H, 8.73. Found: C, 76.89; H, 8.65.

(2*R*,3*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-(1-hexenyl)-3-[(*tert*-butyldimethylsilyl)oxy]-4-(benzyloxy)butane (11b). To a solution of the TBDPS ether **11a** (4.303 g, 8.1 mmol) in 20 mL of dry DMF were added *tert*-butyldimethylsilyl chloride (1.826 g), triethylamine (1.232 g, 1.7 mL), and 4-(dimethylamino)pyridine (149 mg). The solution was stirred at room temperature for 48 h. Then 20 mL of brine was added and the mixture was extracted with ether (3 × 20 mL). The combined ether extracts were washed with saturated NH_4Cl (2 × 10 mL) and dried over $MgSO_4$. After evaporation to dryness, the crude oily product was purified by flash chromatography (hexane/ethyl acetate 50:1), yielding 4.428 g of pure disilyl ether **11b** (81% yield): $[\alpha]^{20}_D$ = −10.13° ($CHCl_3$, c = 2.23); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76–7.27 (m, 15 H, 3 phenyls), 5.42 (dt, 1 H, H-2′, $J_{2',1'}$ = 10.9 Hz, $J_{2',3'}$ = 7.1 Hz), 5.30 (t, 1 H, H-1′, J = 10.4 Hz), 4.50 and 4.46 (d's, 2 H, CH_2-benzyl, J_{gem} = 12.0 Hz), 4.31 (m, 1 H, H-3), 3.71 (t, 1 H, H-1$_1$, J = 9.7 Hz), 3.44 (dd, 1 H, H-1$_2$, J_{gem} = 10.0 Hz, $J_{1_2,2}$ = 5.7 Hz), 3.35, 3.39 (two dd, 2 H, H-4, J_{gem} = 9.2 Hz, $J_{4,3}$ = 6.2 Hz, $J_{4_2,3}$ = 6.4 Hz), 2.73 (m, 1 H, H-2), 1.76 (m, 2 H, H-3′), 1.25–1.10 (m, 6 H, H-4′, H-5′, H-6′), 1.08 (s, 9 H, t-$C_4H_9SiPh_2$), 0.88 (s, 9 H, t-$C_4H_9SiMe_2$), 0.85 (t, 3 H, H-7′, J = 6.6 Hz), 0.11 and 0.09 (2s, 6 H, SiMe_2). Anal. Calcd for $C_{40}H_{60}O_3Si_2$: C, 74.47; H, 9.38. Found: C, 74.57; H, 9.32.

(2*R*,3*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-formyl-3-[(*tert*-butyldimethylsilyl)oxy]-4-(benzyloxy)butane (12). A solution of alkene **11b** (6.065 g, 8.39 mmol) in 60 mL of methylene chloride containing 403 mg of MeOH (1.5 equiv) was cooled to −78 °C, and ozone was passed in until the blue color persisted. Excess ozone was removed by a stream of nitrogen, and then a 10-fold excess of dimethyl sulfide (6.15 mL) was added dropwise. The solution was allowed to warm up to room temperature and stirred for 3 h. After evaporation of solvent, the crude mixture was purified by flash chromatography (hexane/ethyl acetate 50:1) to give 4.625 g of pure aldehyde **12** (84.2% yield): $[\alpha]^{20}_D$ = −12.22° ($CHCl_3$, c = 1.85); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.77 (d, 1 H, CHO, J = 4.0 Hz), 7.64–7.25 (m, 15 H, 3 phenyls), 4.48 (s, 2 H, CH_2-benzyl), 4.39 (m, 1 H, H-3), 4.08 (dd, 1 H, H-1, J_{gem} = 11.0 Hz, $J_{1,2}$ = 6.6 Hz), 3.90 (dd, 1 H, H-1′, J_{gem} = 11.0 Hz, $J_{1',2}$ = 5.5 Hz), 3.46, 3.50 (dd's, 2 H, H-4, J_{gem} = 10.5 Hz, $J_{4,3}$ = 5.5 Hz, $J_{4',3}$ = 5.0 Hz), 2.72 (m, 1 H, H-2), 1.05 (s, 9 H, t-$C_4H_9SiPh_2$), 0.82 (s, 9 H, t-$C_4H_9SiMe_2$), 0.04 and 0.02 (2s, 6 H, $SiMe_2$).

Ozonide 15. A solution of the alkene (302 mg) in 5 mL of methylene chloride was ozonized at −78 °C treated with dimethyl sulfide (10 equiv), and allowed to stir at room temperature for 3 h. Evaporation to dryness yielded a crude oil which was purified over silica gel. Elution with hexane/ethyl acetate (60:1) yielded 46 mg of ozonide followed by 209 mg of aldehyde **12** from elution with hexane/ethyl acetate, 20:1. Rechromatography of the ozonide gave 30 mg of analytically pure ozonide: IR intense bands at 1101 and 1105 cm^{-1}. Anal. Calcd for $C_{40}H_{60}O_6Si_2$: C, 69.31; H, 8.72. Found: C, 69.56, 69.58; H, 8.63, 8.55. The ^{1}H NMR spectrum shows four doublets between δ 5.30 and 5.45 and four triplets between 4.90 and 5.10, all of approximately equal intensity, resulting from the acetalic methine protons and indicating the presence of four diastereomeric ozonides.

Ethyl (3*S*,4*R*,5*S*)-2,2-Difluoro-3-hydroxy-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5-[(*tert*-butyldimethylsilyl)oxy]-6-(benzyloxy)hexanoate (13) and Ethyl (3*R*,4*R*,5*S*)-2,2-Difluoro-3-hydroxy-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5-[(*tert*-butyldimethylsilyl)oxy]-6-(benzyloxy)-hexanoate (14). A suspension of 452 mg of zinc dust in 0.5 mL of dry THF containing 22 μL of 1,2-dibromoethane was heated to 65 °C for 1 min and cooled to 25 °C, after which 27 μL of chlorotrimethylsilane was added. After 15 min, a solution of aldehyde **12** (801 mg, 1.39 mmol) and ethyl bromodifluoroacetate (588 mg, 3.5-fold excess) in 7 mL of THF was added dropwise with external cooling (ice bath). The mixture was stirred for 3 h at room temperature and then quenched with 10 mL of saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and evaporated to dryness. The crude mixture was purified by column chromatography (hexane/ethyl acetate 40:1, 30:1, and 15:1). Two fractions were collected. The 3β isomer **13** (458 mg) was eluted first, followed by the 3α isomer **14** (332 mg): total yield 81.4% (47.2% of β isomer and 34.2% of α isomer), ratio of β:α = 1.38:1.

3β isomer: $[\alpha]^{20}_D$ = −19.2° ($CHCl_3$, c = 1.51); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64–7.21 (m, 15 H, 3 phenyls), 4.58 (dm, 1 H, H-3, $J_{H,F}$ = 23.4 Hz), 4.41 (q, 1 H, H-5, J = 5.0 Hz), 4.36 and 4.30 (d's, 2 H, CH_2-benzyl, J = 12.2 Hz), 4.32 (q, 2 H, $CO_2CH_2CH_3$, J = 7.1 Hz), 4.28 (d, 1 H, OH, J = 6.1 Hz), 4.16 (dd, 1 H, H-6, J_{gem} = 11.1 Hz, $J_{6,4}$ = 6.0 Hz), 3.93 (dd, 1 H, H-6′, J_{gem} = 11.1 Hz, $J_{6',4}$ = 3.6 Hz), 3.44 (dd, 1 H, H-7, J_{gem} = 10.2 Hz, $J_{7,5}$ = 4.3 Hz), 3.30 (dd, 1 H, H-7′, J_{gem} = 10.2 Hz, $J_{7',5}$ = 5.1 Hz), 2.22 (m, 1 H, H-4), 1.35 (t, 3 H, $CO_2CH_2CH_3$, J = 7.2 Hz), 1.10 (s, 9 H, t-$C_4H_9SiPh_2$), 0.88 (s, 9 H, t-$C_4H_9SiMe_2$), 0.13 and 0.09 (2s, 6 H, SiMe_2); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 112.37 (dd, $J_{F,F}$ = 259 Hz, $J_{H,F}$ = 5 Hz), 122.69 (dd, $J_{F,F}$ = 258 Hz, $J_{H,F}$ = 22 Hz). Anal. Calcd for $C_{38}H_{54}O_6F_2Si_2$: C, 65.10; H, 7.76. Found: C, 64.95; H, 7.67.

3α isomer: $[\alpha]^{20}_D$ = +5.4° ($CHCl_3$, c = 1.7); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68–7.25 (m, 15 H, 3 phenyls), 4.73 (d, 1 H, OH, J = 6.6 Hz), 4.51, 4.46 (dd, 2 H, CH_2-benzyl, J_{gem} = 11.9 Hz), 4.54–4.43 (m, 2 H, H-5 and H-3), 4.35 (dq, 2 H, $CO_2CH_2CH_3$, J = 6.9 Hz), 3.86 (m, 2 H, H-6), 3.45, 3.42 (dd's, 2 H, H-7, J_{gem} = 9.5 Hz, $J_{7,5}$ = 5.7 Hz, $J_{7',5}$ = 7.2 Hz), 2.35 (m, 1 H, H-4), 1.35 (t, 3 H, $CO_2CH_2CH_3$, J = 7.2 Hz), 1.08 (s, 9 H, t-$C_4H_9SiPh_2$), 0.86 (s, 9 H, t-$C_4H_9SiMe_2$), 0.08 and 0.06 (2s, 6 H, SiMe_2); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 111.02 (dd, $J_{F,F}$ = 259.4 Hz, $J_{H,F}$ = 5.8 Hz), 122.21 (dd, $J_{F,F}$ = 259.4 Hz, $J_{H,F}$ = 23 Hz). Anal. Calcd for $C_{38}H_{54}O_6F_2Si_2$: C, 65.10; H, 7.76. Found: C, 65.11; H, 7.78.

(3*R*,4*R*,5*S*)-1-Oxo-2,2-difluoro-3α-hydroxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (17). A solution of the α epimer **14** (0.3 g, 0.428 mmol) in 50 mL of AcOH/H_2O (9:1) was stirred at 65 °C for 2 days. At the end of this period, the AcOH and H_2O were distilled off under vacuum to give **17** (0.220 g, 95%), which was used in the subsequent reaction without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73–7.17 (m, 15 H, 3 phenyls), 4.76 (m, 1 H, H-3), 4.56 (m, 1 H, H-5), 4.50 and 4.37 (dd, 2 H, CH_2-benzyl, J_{gem} = 12.1 Hz), 3.89 (dd, 1 H, H-7, J_{gem} = 10.6 Hz, $J_{4,7}$ = 3.6 Hz), 3.79 (dd, 1 H, H-7′, J_{gem} = 10.6 Hz, $J_{4,7'}$ = 6.2 Hz), 3.64 (dd, 1 H, H-8, J_{gem} = 11.6 Hz, $J_{5,8}$ = 2.2 Hz), 3.32 (dd, 1 H, H-8′, J_{gem} = 11.6 Hz, $J_{5,8'}$ = 2.9 Hz), 2.75 (m, 1 H, H-4), 1.15 (s, 9 H, t-$C_4H_9SiPh_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 107.42 (d, $J_{F,F}$ = 286.0 Hz), 120.98 (d, $J_{F,F}$ = 286.0 Hz).

(3*R*,4*R*,5*S*)-1-Hydroxy-2,2-difluoro-3α-hydroxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (18). To a solution of the lactone **17** (0.220 g, 0.407 mmol) in 15 mL of methanol at 22 °C was added 0.062 g of $NaBH_4$ (1.629 mmol, 4 equiv) in three portions. The mixture was stirred for 30 min at 22 °C and quenched with 10 mL of saturated aqueous NaCl solution. This was extracted with EtOAc (4 × 15 mL), which was dried (Na_2SO_4) and evaporated to give **18** (0.215 g, 97%). This material was directly used in the next reaction. The ^{1}H NMR spectrum indicated a mixture of anomers.

(1*S*,3*R*,4*R*,5*S*)-1β-(Mesyloxy)-2,2-difluoro-3α-hydroxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (19). A solution of the anomeric lactols **18** (0.215 g, 0.396 mmol) in pyridine (0.313 g, 3.96 mmol) and 100 mg of 4-Å molecular sieves powder was stirred at 22 °C for 30 min. To this was added methanesulfonyl chloride (0.135 g, 1.188 mmol) dropwise with stirring, which was continued for an additional hour. The mixture was diluted with 10 mL of EtOAc and filtered through a pad of Celite. The EtOAc extract was concentrated, and the crude product obtained was purified by flash column chromatography using hexane/EtOAc (4:1) as eluant to give pure β-mesylate **19**: yield, 0.220 g (89%); $[\alpha]^{20}_D$ = +8.96° (c = 1.35 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65–7.13 (m, 15 H, 3 phenyls), 5.82 (d, 1 H, H-1, $J_{H,F}$ = 15.4 Hz), 4.45 (m, 1 H, H-3), 4.41 and 4.32 (d's, 2 H, CH_2-benzyl, J_{gem} = 12.2 Hz), 4.23 (m, 1 H, H-5), 3.85 (dd, 1 H, H-7, J_{gem} = 10.6 Hz, $J_{4,7}$ = 4.0 Hz), 3.75 (dd, 1 H, H-7′, J_{gem} = 10.6 Hz, $J_{4,7'}$ = 6.2 Hz), 3.54 (dd, 1 H, H-8, J_{gem} = 11.2 Hz, $J_{5,8}$ = 2.3 Hz), 3.32 (dd, 1 H, H-8′, J_{gem} = 11.2 Hz, $J_{5,8'}$ = 5.0 Hz), 3.14 (s, 3 H, OSO_2CH_3), 2.31 (m, 1 H, H-4), 1.10 (s, 9 H, t-$C_4H_9SiPh_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 126.62 (dd, $J_{F,F}$ = 253.0 Hz, $J_{H,F}$ = 8.7 Hz), 130.92 (dd, $J_{F,F}$ = 253.0 Hz, $J_{H,F}$ = 15.3 Hz).

(1*R*,3*R*,4*R*,5*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (20). To a stirred solution of the mesylate **19** (0.220 g, 0.354 mmol) in 35.5 mL of MeOH/H_2O (4:1) was added potassium carbonate (0.244 g, 1.774 mmol), and stirring was continued overnight (15 h). The solution was then concentrated under vacuum to remove most of the methanol, and the concentrate was extracted with EtOAc (5 × 20 mL). The EtOAc extract was dried (Na_2SO_4), and the solvent was removed under vacuum. Purification by flash chromatography gave pure **20** (0.143 g, 77%): $[\alpha]^{20}_D$ = +23.96° (c = 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60–7.20 (m, 15 H, 3 phenyls), 5.62 (d, 1 H, H-1, $J_{1,3}$ = 4.4 Hz), 5.04 (dd, 1 H, H-3, $J_{1,3}$ = 4.4 Hz, $J_{H,F}$ = 8.5 Hz), 4.52 (s, 2 H, CH_2-benzyl), 3.88 (dt, 1 H, H-5, $J_{5,9}$ = 4.0 Hz, $J_{4,5}$ = $J_{5,9'}$ = 6.8 Hz), 3.80 (dd, 1 H, H-8, J_{gem} = 9.9 Hz, J = 9.1 Hz), 3.70 (dd, 1 H, H-8′, J_{gem} = 9.9 Hz, $J_{4,8'}$ = 6.2 Hz), 3.6 (dd, 1 H, H-9, J_{gem} = 10.2 Hz, $J_{5,9}$ = 6.9 Hz), 3.46 (dd, 1 H, H-9′, J_{gem} = 10.2 Hz, $J_{5,9'}$ = 4.0 Hz), 2.34 (q, 1 H, H-4, J = 7.06), 1.05 (s, 9 H, t-$C_4H_9SiPh_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ

108.51 (d, $J_{F,F}$ = 186.3 Hz), 137.37 (dd, $J_{F,F}$ = 186.3 Hz, $J_{H,F}$ = 8.5 Hz); HRMS calcd $C_{13}H_{13}O_4F_2Si$ (M − $CH_2C_6H_5$ − C_6H_5 − tBu, 29) 299.0551, *m/z* 299.0543. Anal. Calcd for $C_{30}H_{34}O_4F_2Si_2$: C, 68.67; H, 6.53. Found: C, 68.59; H, 6.58.

(1*R*,3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-5-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (21). To a solution of the silyl ether **20** (0.160 g, 0.305 mmol) in 10 mL of dry THF was added 458 μL of 1.0 M tetrabutylammonium fluoride in THF, dropwise at 0 °C with stirring. Stirring was continued for 30 min at 0 °C, and the solution was quenched with 10 mL of saturated aqueous NaCl solution and then extracted with EtOAc (5 × 15 mL). The EtOAc extract was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography using hexane:EtOAc = 85:15 as eluant gave **21** (0.071 g, 82%): $[\alpha]^{20}_D$ = +20.51° (*c* = 0.98 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.28 (m, 5 H, one phenyl), 5.64 (d, 1 H, H-1, $J_{1,3}$ = 4.5 Hz), 4.96 (dd, 1 H, H-3, $J_{1,3}$ = 4.5 Hz, $J_{H,F}$ = 8.4 Hz), 4.61 (s, 2 H, CH_2-benzyl), 4.04 (q, 1 H, H-5, *J* = 6.2 Hz), 3.79 (m, 2 H, H-8, H-8′), 3.74 (dd, 1 H, H-9, J_{gem} = 10.0 Hz, $J_{5,9}$ = 5.9 Hz), 3.60 (dd, 1 H, H-9′, J_{gem} = 10.0 Hz, $J_{5,9'}$ = 5.8 Hz), 2.40 (q, 1 H, 6.7 Hz, H-4), 2.03 (bs, 1 H, OH); ^{19}F NMR ($CDCl_3$, 376.2 MHz) φ 108.62 ($J_{F,F}$ = 182.3 Hz), 137.52 (dd, $J_{F,F}$ = 182.3 Hz, $J_{H,F}$ = 8.4 Hz). Anal. Calcd for $C_{14}H_{16}O_4F_2$: C, 58.73; H, 5.63. Found: C, 58.89; H, 5.80.

Preparation of 21 from the 3β-Alcohol 13. Ethyl (3*S*,4*R*,5*S*)-2,2-Difluoro-3-(mesyloxy)-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5-[(*tert*-butyldimethylsilyl)oxy]-6-(benzyloxy)hexanoate (26). To a solution of the 3β-alcohol **13** (0.10 g, 0.142 mmol) in pyridine (0.112 g, 1.42 mmol) stirred at 22 °C was added methanesulfonyl chloride (0.065 g, 0.57 mmol), and the reaction mixture was stirred overnight. This mixture was diluted with ether, and the ether extract was filtered through a Celite pad and concentrated. The crude material was flash chromatographed to give the pure mesylate **26** (0.110 g, 99%): $[\alpha]^{20}_D$ = +0.5° (*c* = 2.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67–7.22 (m, 15 H, 3 phenyls), 5.54 (dt, 1 H, H-3, *J* = 1.5 Hz, *J* = 12.3 Hz), 4.40 (s, 2 H, CH_2-benzyl), 4.35 (q, 1 H, H-5, *J* = 5.1 Hz), 4.20 (q, 2 H, CH_2CH_3, *J* = 7.0 Hz), 3.91 (dd, 1 H, H-6, J_{gem} = 10.7 Hz, $J_{4,6}$ = 4.1 Hz), 3.81 (dd, 1 H, H-6′, J_{gem} = 10.7 Hz, $J_{4,6'}$ = 7.3 Hz), 3.62 (dd, 1 H, H-7, J_{gem} = 10.1 Hz, $J_{5,7}$ = 5.2 Hz), 3.48 (dd, 1 H, H-7′, J_{gem} = 10.1 Hz, $J_{5,7'}$ = 5.4 Hz), 2.95 (s, 3 H, OSO_2CH_3), 2.40 (m, 1 H, H-4), 1.3 (t, 3 H, CH_2CH_3), 1.10 (s, 9 H, *t*-$C_4H_9SiPh_2$), 0.9 (s, 9 H, *t*-$C_4H_9SiMe_2$), 0.12 (s, 6 H, 2 CH_3); ^{19}F NMR ($CDCl_3$, 376.0 MHz) φ 130.0 (s).

(3*S*,4*R*,5*S*)-1-Oxo-2,2-difluoro-3β-(mesyloxy)-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (27). A solution of the mesylate **26** (0.110 g, 0.141 mmol) in 20 mL of AcOH/H_2O (9:1) was stirred at 65 °C for 2 days. The solvent was distilled off under vacuum to give lactone **27** (0.085 g, 97%), which was used in the subsequent reaction without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75–7.12 (m, 15 H, 3 phenyls), 5.47 (m, 1 H, H-3), 4.58 (m, 1 H, H-5), 4.37 and 4.24 (d's, 2 H, CH_2-benzyl, J_{gem} = 12.0 Hz), 4.03 (dd, 1 H, H-7, J_{gem} = 11.4 Hz, $J_{4,7}$ = 2.5 Hz), 3.58 (d, 1 H, H-7′, J_{gem} = 11.4 Hz), 3.50 (dd, 1 H, H-8, J_{gem} = 11.6 Hz, $J_{5,8}$ = 1.3 Hz), 3.15 (s, 3 H, OSO_2CH_3), 3.05 (dd, 1 H, H-8′, J_{gem} = 11.6 Hz, $J_{5,8'}$ = 3.0 Hz), 2.70 (m, 1 H, H-4), 1.10 (s, 9 H, *t*-$C_4H_9SiPh_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) δ 126.38 (dd, $J_{F,F}$ = 280 Hz, $J_{H,F}$ = 10.0 Hz), 130.9 (dd, $J_{F,F}$ = 280 Hz, $J_{H,F}$ = 12.0 Hz).

(3*S*,4*R*,5*S*)-1-Hydroxy-2,2-difluoro-3β-(mesyloxy)-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (28). Sodium borohydride (0.016 g, 0.420 mmol) was added in two portions to a solution of the lactone **27** (0.065 g, 0.105 mmol) in 1 mL of methanol. The mixture was stirred for 30 min and quenched with 2 mL of saturated aqueous NaCl solution. The crude reaction mixture was extracted with EtOAc (5 × 3 mL), the EtOAc was dried (Na_2SO_4) and concentrated, and the residue was flash chromatographed using EtOAc/hexane (1:4) as eluant: yield (mixture of α and β anomers), 51 mg (78%); $[\alpha]^{20}_D$ = +10.66° (*c* = 0.9 in $CHCl_3$).

α anomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.68–7.15 (m, 15 H, 3 phenyls), 5.61 (ddd, 1 H, H-3, $J_{H,F}$ = 20.2 Hz, $J_{H,F}$ = 3.0 Hz, $J_{3,4}$ = 11.4 Hz), 5.27 (broad t, 1 H, H-1, *J* = 3.5–4.5 Hz), 4.40 (m, 1 H, H-5), 4.38 and 4.16 (dd's, 2 H, CH_2-benzyl, J_{gem} = 12.10 Hz), 4.13 (d, 1 H, OH, *J* = 7.1 Hz), 3.95 (dd, 1 H, H-7, J_{gem} = 11.3 Hz, $J_{4,7}$ = 2.1 Hz), 3.50 (dd, 1 H, H-7′, J_{gem} = 11.6 Hz, $J_{4,7'}$ = 1.7 Hz), 3.33 (dd, 1 H, H-8, J_{gem} = 11.1 Hz, $J_{5,8}$ = 1.5 Hz), 3.12 (s, 3 H, OSO_2CH_3), 3.05 (dd, 1 H, H-8′, J_{gem} = 11.1 Hz, $J_{5,8'}$ = 5.2 Hz), 2.22 (m, 1 H, H-4), 1.10 (s, 9 H, *t*-$C_4H_9SiPh_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) φ 133.88 (dm, $J_{F,F}$ = 242 Hz), 139.8 (dd, $J_{F,F}$ = 242 Hz, $J_{H,F}$ = 22 Hz, $J_{H,F}$ = 2.5 Hz).

β anomer: ^{1}H NMR δ 7.68–7.15 (m, 15 H, 3 phenyls), 5.29 (m, 1 H, H-3), 4.72 (br d, 1 H, H-1, $J_{H,F}$ = 15.1 Hz), 4.40 (m, 1 H, H-5), 4.33 and 4.15 (d's, 2 H, CH_2-benzyl, J_{gem} = 12.10 Hz), 3.95 (m, 1 H, H-7), 3.79 (dd, 1 H, H-7′, J_{gem} = 10.3 Hz, $J_{4,7'}$ = 2.4 Hz), 3.40 (dd, 1 H, H-8, J_{gem} = 11.0 Hz, $J_{5,8}$ = 1.2 Hz), 3.17 (s, 3 H, OSO_2CH_3), 2.97 (dd, 1 H, H-8′, J_{gem} = 11.0 Hz, $J_{5,8'}$ = 4.1 Hz), 2.24 (m, 1 H, H-4), 1.10 (s, 9 H, *t*-$C_4H_9SiPh_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) φ 134.04 (dm, $J_{F,F}$ = 246.7 Hz), 139.8 (dm, $J_{F,F}$ = 246.7 Hz).

(1*R*,3*R*,4*R*,5*S*)-4-(Hydroxymethyl)-5-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (21). To a solution of the anomeric mesylates **28** (12 mg, 0.0193 mmol) in 150 μL of DMF were added hexamethylphosphoric triamide (7.62 mg, 0.0425 mmol) and 42.5 μL (0.0425 mmol) of 1.0 M LiN $(TMS)_2$ in THF solution, and the mixture was heated to 60 °C for 20 h. At the end of this period, it was quenched with 0.5 mL of saturated aqueous NH_4Cl solution and extracted with hexane (10 × 2 mL). The hexane extract was dried (Na_2SO_4), filtered, and concentrated. The NMR spectrum indicated that the residue was a mixture of **20** and **21** (4:1). Hence, the residue was dissolved in 0.5 mL of THF and cooled to 0 °C (ice bath). To this was added 19 μL (0.019 mmol) of 1.0 M tetrabutylammonium fluoride in THF, and the mixture was stirred at 0 °C for 30 min. It was quenched with 1.0 mL of saturated aqueous NH_4Cl solution and extracted with EtOAc (5 × 2 mL). The EtOAc extract was dried (Na_2SO_4), filtered, and concentrated and the crude material was flash chromatographed to give pure **21**: yield, 4.4 mg (80% from **28**). Its ^{1}H and ^{19}F NMR spectra were identical with those for the material derived from the 3α-hydroxy-1β-mesylate **19**. When the reaction of **28** with base was conducted for shorter periods of time, the pure α anomer of **28** was isolated together with **21**.

(1*R*,3*R*,4*R*,5*S*)-4-[[(*p*-Tolylsulfonyl)oxy]methyl]-5-[(benzyloxy)-methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (22). To a solution of alcohol **21** (0.070 g, 0.246 mmol) in pyridine (1.99 mL, 24.6 mmol) were added 4-(dimethylamino)pyridine (0.309 g, 2.53 mmol) and *p*-toluenesulfonyl chloride (0.365 g, 1.92 mmol), and the reaction mixture was stirred at 22 °C for 36 h. This mixture was diluted with ether and filtered through a pad of silica gel, and the ether extract was concentrated. After flash chromatography, pure **22** (0.086 mg, 79%) was obtained: $[\alpha]^{20}_D$ = +42.45° (*c* = 1.02 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, 2 H, tosyl, *J* = 8.2 Hz), 7.38–7.28 (m, 7 H, phenyl + tosyl), 5.60 (d, 1 H, H-1, $J_{1,3}$ = 4.2 Hz), 4.90 (dd, 1 H, H-3, $J_{1,3}$ = 4.2 Hz, $J_{H,F}$ = 8.2 Hz), 4.56 and 4.55 (d's, 2 H, CH_2-benzyl, J_{gem} = 12.2 Hz), 4.15 (m, 2 H, H-5, H-8), 3.82 (q, 1 H, H-8′, *J* = 6.5 Hz), 3.67 (dd, 1 H, H-9, J_{gem} = 9.9 Hz, $J_{5,9}$ = 5.8 Hz), 3.54 (dd, 1 H, H-9′, J_{gem} = 9.9 Hz, $J_{5,9'}$ = 5.7 Hz), 2.60 (m, 1 H, H-4), 2.45 (s, 3 H, $C_6H_4CH_3$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) φ 108.50 (d, $J_{F,F}$ = 184.8 Hz), 137.49 (dd, $J_{F,F}$ = 184.8 Hz, $J_{H,F}$ = 8.2 Hz); HRMS calcd for $C_{21}H_{22}O_6F_2S$ (M^+, 26) 440.1105, *m/z* 440.1095.

(1*R*,3*R*,4*R*,5*S*)-4-(Cyanomethyl)-5-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (23). A solution of tosylate **22** (0.086 g, 0.195 mmol) and sodium cyanide (0.095 g, 1.95 mmol) in DMF (1 mL) was stirred under nitrogen at 42 °C for 26 h. The solution was worked up by dilution with ethyl ether, and the resulting precipitate was filtered through a pad of Celite. The filtrate was concentrated and flash chromatographed (15% EtoAc/85% hexane) to give pure nitrile **23** (0.0465 g, 81%): $[\alpha]^{20}_D$ = +22.93° (*c* = 0.75 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.30 (m, 5 H, one phenyl), 5.67 (d, 1 H, H-1, $J_{1,3}$ = 4.2 Hz), 4.96 (dd, 1 H, H-3, $J_{1,3}$ = 4.2 Hz, $J_{H,F}$ = 8.1 Hz), 4.60 and 4.58 (d's, 2 H, CH_2-benzyl, J_{gem} = 11.9 Hz), 3.89 (q, 1 H, H-5, *J* = 6.2 Hz), 3.74 (dd, 1 H, H-9, J_{gem} = 9.8 Hz, $J_{5,9}$ = 5.1 Hz), 3.60 (dd, 1 H, H-9′, J_{gem} = 9.8 Hz, $J_{5,9'}$ = 6.8 Hz), 2.67 (m, 3 H, H-4, H-8, H-8′); ^{19}F NMR ($CDCl_3$, 376.2 MHz) φ 108.37 (d, $J_{F,F}$ = 184.3 Hz), 137.07 (dd, $J_{F,F}$ = 184.3 Hz, $J_{H,F}$ = 8.1 Hz); HRMS calcd for $C_{15}H_{15}F_2NO_3$ (M^+, 57) 295.1020, *m/z* 295.1033.

(1*R*,3*R*,4*R*,5*S*)-4-(Cyanomethyl)-5-(hydroxymethyl)-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (24). To a suspension of 10% palladium on carbon (5 mg) in isopropyl alcohol (0.5 mL) was added benzyl ether **23** (12 mg, 0.040 mmol), and after evacuation, hydrogen was admitted. After the mixture was stirred at 22 °C for 30 h, the crude nitrile alcohol was recovered by passing the reaction mixture through a Celite pad, eluting with EtOAc, and concentrating the EtOAc extract. Pure **24** (6.9 mg, 83%) was obtained after flash chromatography of the crude material: $[\alpha]^{20}_D$ = +52.20° (*c* = 0.5 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.71 (d, 1 H, H-1, $J_{1,3}$ = 4.3 Hz), 4.98 (dd, 1 H, H-3, $J_{1,3}$ = 4.3 Hz, $J_{H,F}$ = 8.2 Hz), 3.90 (m, 1 H, H-5), 3.87 (m, 1 H, H-9), 3.80 (m, 1 H, H-9′), 2.81 (q, 1 H, H-4, *J* = 6.9 Hz), 2.66 (m, 2 H, H-8, H-8′), 1.88 (m, 1 H, OH); ^{19}F NMR ($CDCl_3$, 376.2 MHz) φ 108.99 (d, $J_{F,F}$ = 188.0 Hz), 136.62 (dd, $J_{F,F}$ = 188 Hz, $J_{H,F}$ = 8.2 Hz). Anal. Calcd for $C_8H_9NO_3F_2$: C, 46.83; H, 4.42. Found: C, 46.51; H, 4.62.

(1*R*,3*R*,4*R*,5*S*)-4-(Cyanomethyl)-5-(acetoxymethyl)-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (24A). A solution of alcohol **24** (2.0 mg, 9.7 μmol) in triethylamine (9.85 mg, 9.7 μmol) was stirred at 22 °C for 5 min. To this solution was added acetic anhydride (3.17 mg, 24.39 μmol) in 100 μL of CH_2Cl_2, and stirring was continued for 3 h in 22 °C. The reaction mixture was quenched with 0.5 mL of water and extracted with CH_2Cl_2 (3 × 2 mL). The CH_2Cl_2 extract was dried (Na_2SO_4) and concentrated. The crude product was flash chromatographed to give pure acetate **24A** (2.4 mg, 100%): $[\alpha]^{20}_D$ = +29.16° (*c* = 0.24 in $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.70 (d, 1 H, H-1, $J_{1,3}$ = 4.4 Hz), 4.97 (dd, 1 H, H-3, $J_{1,3}$ = 4.4 Hz, $J_{H,F}$ = 7.4 Hz), 4.36 (dd, 1 H, H-9, J_{gem} = 12.1 Hz, $J_{5,9}$ = 4.1 Hz), 4.25 (dd, 1 H, H-9′, J_{gem} = 12.1 Hz, $J_{5,9'}$ = 5.9 Hz), 3.96 (m, 1 H, H-5), 2.68 (m, 2 H, H-8), 2.62 (m, 1 H, H-4), 2.13 (s, 3 H, OAc); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 108.8 (d, $J_{F,F}$ = 187.3 Hz), 137.06 (dd, $J_{F,F}$ = 187.3 Hz, $J_{H,F}$ = 7.2 Hz); HRMS calcd for $C_8H_{11}NO_4F_2$ ($M^+ - CH_3CO_2H$, 5) 187.0444, m/z 187.0458.

The above spectra are identical with those reported earlier for the product prepared by the PLE procedure.[11] The specific rotation of this product is 4° higher.

(1*R*,3*R*,4*R*,5*S*)-4-(Oxoethyl)-5-(hydroxymethyl)-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (25). A solution of the nitrile **24** (0.017 g, 0.082 mmol) in 500 μL of dry CH_2Cl_2 was cooled to −26 °C (dry ice/CCl_4 bath), and 1.0 M DIBAL-H in hexane (124 μL, 0.124 mmol) was added. The mixture was stirred at 26 °C for 2 h, quenched with 0.5 mL of saturated aqueous NH_4Cl solution and several drops of 1.0 N HCl to lower the pH to 3.0, and stirred until the solution became clear. The solution was extracted with CH_2Cl_2 (10 × 1 mL), the CH_2Cl_2 extract was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under a slow stream of N_2 at −5 °C: yield, 13.5 mg (80%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.77 (s, 1 H, CHO), 5.66 (d, 1 H, H-1, $J_{1,3}$ = 4.4 Hz), 4.84 (dd, 1 H, H-3, $J_{H,F}$ = 8.5 Hz, $J_{1,3}$ = 4.4 Hz), 3.88 (m, 1 H, H-5), 3.81 (m, 1 H, H-9), 3.72 (m, 1 H, H-9′), 2.94 (m, 1 H, H-4), 2.89 (m, 1 H, H-8), 2.72 (m, 1 H, H-8′), 1.94 (m, 1 H, OH). For completion of the synthesis, see supplementary material to ref 11.

Preparation of 9β,11β-Oxido-10,10-difluorothromboxane A_2. (3*S*,4*R*,5*S*)-1-Oxo-2,2-difluoro-3β-hydroxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (29). A solution of the β epimer **13** (1.670 g, 2.39 mmol) in 200 mL of 90% AcOH/H_2O (9:1) was stirred at 65 °C for 48 h. At the end of this period, the temperature was raised to 80 °C, and the AcOH/H_2O was distilled to dryness under vacuum. Methylene chloride was added to the residue, and the solvent was removed under nitrogen. The crude lactone **29** (1.57 g) was used in the subsequent reaction without further purification. The ^{1}H NMR spectrum showed partial desilylation (ca. 10%) of the lactone. Assignments of the signals for the methylene protons at C-7 and C-8 are based on double irradiation experiments. **29**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.20 (m, 15 H, 3 phenyls), 4.65 (dm, 1 H, H-5, J = 10.0 Hz), 4.52 and 4.41 (d's, 2 H, CH_2-benzyl, J_{gem} = 12.1 Hz), 4.32 (m, 1 H, H-3), 3.97 (dd, 1 H, H-7, J_{gem} = 10.8 Hz, $J_{7,4}$ = 3.1 Hz), 3.68 (m, 2 H, H-7′, H-8′), 3.49 (dd, 1 H, H-8, J_{gem} = 11.5 Hz, $J_{8,5}$ = 3.6 Hz), 2.47 (m, 1 H, H-4), 1.08 (s, 9 H, *t*-C$_4H_9$SiPh$_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 113.60 (dd, $J_{F,F}$ = 274.8 Hz, $J_{H,F}$ = 10 Hz), 118.27 (dd, $J_{F,F}$ = 274.8 Hz, $J_{H,F}$ = 12 Hz).

(3*S*,4*R*,5*S*)-1-Oxo-2,2-difluoro-3β-acetoxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (30). To the solution of the crude lactone **29** (1.570 g, 2.90 mmol) in 15 mL of pyridine was added 0.8 mL of acetic anhydride. The mixture was allowed to stand overnight at 22 °C and evaporated to dryness in vacuo. The crude oily product **30** was obtained (1.654 g, 98% yield), which was used in the next step without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71–7.19 (m, 15 H, 3 phenyls), 5.72 (m, 1 H, H-3), 4.71 (br d, 1 H, H-5, J = 10.3 Hz), 4.49 and 4.37 (d's, 2 H, J_{gem} = 11.8 Hz, CH_2-benzyl), 3.78 (br, 1 H, H-7, J = 11.1 Hz), 3.68 (br, 1 H, H-8, J = 11.6 Hz), 3.61 (br d, 1 H, H-7′, J = 11.1 Hz), 3.41 (dd, 1 H, H-8′, J_{gem} = 11.6 Hz, $J_{8',5}$ = 2.9 Hz), 2.58 (m, 1 H, H-4), 2.08 (s, 3 H, OAc), 1.08 (s, 9 H, *t*-C$_4H_9$SiPh$_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 111.41 (dd, $J_{F,F}$ = 280.8 Hz, $J_{H,F}$ = 10.0), 116.35 (dd, $J_{F,F}$ = 280.8 Hz, $J_{H,F}$ = 9.2 Hz).

(3*S*,4*R*,5*S*)-1α-Hydroxy-2,2-difluoro-3β-acetoxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (31). To the solution of crude lactone **30** (1.654 g, 2.84 mmol) in 50 mL of methanol was added portionwise 500 mg (4.5-fold excess) of sodium borohydride. The mixture was stirred at room temperature for 20 min, and then 50 mL of brine was added. Methanol was evaporated at room temperature on a rotary evaporator, and the aqueous phase was extracted with ethyl acetate (5 × 20 mL). The combined ethyl acetate extracts were dried over $MgSO_4$ and evaporated to dryness, leaving 1.593 g of crude lactol **31** (96% yield) which was used in the next step without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56–7.20 (m, 15 H, 3 phenyls), 5.83 (ddd, 1 H, H-3, $J_{H,F}$ = 3.7, 21.2 Hz, $J_{H,H}$ = 11.5 Hz), 5.25 (d, 1 H, H-1, $J_{H,F}$ = 5.3 Hz), 4.52 and 4.40 (d's, 2 H, CH_2-benzyl, J_{gem} = 12.2 Hz), 4.40 (m, 1 H, H-5), 3.67 (dd, 1 H, H-7, J_{gem} = 10.8 Hz, $J_{7,4}$ = 1.4 Hz), 3.57 (dd, 1 H, H-8, J_{gem} = 11.2 Hz, $J_{8,5}$ = 3.1 Hz), 3.46 (m, 2 H, H-7′, H-8′), 2.19 (m, 1 H, H-4), 2.0 (s, 3 H, OAc), 1.08 (s, 9 H, *t*-C$_4H_9$SiPh$_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 121.20 (d, $J_{F,F}$ = 244.2 Hz), 123.60 (dd, $J_{F,F}$ = 247.3 Hz, $J_{H,F}$ = 3.7 Hz).

(3*S*,4*R*,5*S*)-1α-(Mesyloxy)-2,2-difluoro-3β-acetoxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-[(benzyloxy)methyl]-1,5-oxidopentane (32). To the solution of the lactol **31** (1.593 g, 2.73 mmol) in 40 mL of methylene chloride was added triethylamine (600 μL) under nitrogen. The resulting mixture was stirred at room temperature for 30 min, and after it was cooled to 0 °C, mesyl chloride (270 μL) was added via syringe. The mixture was stirred at 0 °C for 10 min and then quenched with 20 mL of water. The methylene chloride layer was separated, and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated to dryness, leaving 1.541 g of crude mesylate **32** (85%) which was used for cyclization without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70–7.20 (m, 15 H, 3 phenyls), 5.90 (d, 1 H, H-1, $J_{H,F}$ = 4.5 Hz), 5.82 (ddd, 1 H, H-3, $J_{H,F}$ = 4.9, 20.2 Hz, $J_{H,H}$ = 11.4 Hz), 4.48 and 4.34 (d's, 2 H, CH_2-φ, J_{gem} = 11.9 Hz), 4.45 (m, 1 H, H-5), 3.62 (d, 1 H, H, J_{gem} = 11.3 Hz), 3.62 (d, 1 H, H-8, J_{gem} = 11.3 Hz), 3.51 (br, 1 H, H-7′, J = 11.3 Hz), 3.39 (dd, 1 H, H-8′, J_{gem} = 11.3 Hz, $J_{8',5}$ = 4.6 Hz), 3.13 (s, 3 H, SO_2CH_3), 2.33 (m, 1 H, H-4), 2.04 (s, 3 H, OAc), 1.10 (s, 9 H, *t*-C$_4H_9$SiPh$_2$); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 120.79 (dds, $J_{F,F}$ = 249.2 Hz, $J_{H,F}$ = 5 Hz), 121.87 (dd, $J_{F,F}$ = 249.2 Hz, $J_{H,F}$ = 4 Hz).

(1*S*,3*S*,4*R*,5*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (33). A solution of 1.541 g of mesylate **32** (2.32 mmol) in 251 mL of 0.05 M aqueous methanolic (methanol/water v/v 4:1) potassium carbonate (5 equiv of K_2CO_3) was stirred for 16 h at room temperature. Methanol was evaporated on rotary evaporator at room temperature, and the aqueous phase was extracted with ethyl acetate (5 × 30 mL). After drying over $MgSO_4$ and evaporation to dryness, 1.350 g of crude **33** was obtained (partially desilylated), which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61–7.22 (m, 15 H, 3 phenyls), 5.59 (m, 1 H, H-1), 4.98 (m, 1 H, H-3), 4.53 (s, 2 H, CH_2-benzyl), 4.08 (m, 1 H, H-5), 3.68 (m, 1 H, H-9), 3.62 (dd, 1 H, H-8, J_{gem} = 11.1 Hz, $J_{8',4}$ = 5.5 Hz), 3.54 (dd, 1 H, H-8′, J_{gem} = 10.5 Hz, $J_{8',4}$ = 6.6 Hz), 3.47 (dd, 1 H, H-9′, J_{gem} = 10.5 Hz, $J_{9',5'}$ = 3.9 Hz), 2.76 (m, 1 H, H-4), 1.06 (s, 9 H, *t*-C$_4H_9$SiPh$_2$).

(1*S*,3*S*,4*R*,5*S*)-4-(Hydroxymethyl)-5-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (34). To the solution of silyl ether **33** (1.350 g) in 20 mL of dry THF cooled to 0 °C was added dropwise 2.5 mL of a 1 M solution of tetrabutylammonium fluoride. The solution was stirred for 15 min at 0 °C and quenched with 20 mL of brine. The mixture was extracted with ethyl acetate (5 × 15 mL), and the combined extracts were dried over $MgSO_4$ and evaporated to dryness. The crude alcohol **34** was purified by flash chromatography (3:1 hexane/ethyl acetate). The pure alcohol **34** (405 mg, 61% from **32**) was obtained: $[\alpha]^{20}_D$ = +1.91° ($CHCl_3$, c = 1.49); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.30 (m, 5 H, phenyl), 5.59 (m, 1 H, H-1), 4.91 (m, 1 H, H-3), 4.62 (s, 2 H, CH_2-benzyl), 4.23 (m, 1 H, H-5), 3.71 (dd, 1 H, H-9, J_{gem} = 10.5 Hz, $J_{9,5}$ = 5.5 Hz), 3.68 (m, 2 H, H-8), 3.60 (dd, 1 H, H-9′, J_{gem} = 10.5 Hz, $J_{9',5}$ = 6.2 Hz), 2.79 (m, 1 H, H-4); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 103.76 (d, $J_{F,F}$ = 190.0 Hz), 132.89 (dm, $J_{F,F}$ = 190.0 Hz); HRMS calcd for $C_{14}H_{16}O_4F_2$ (M^+, 2) 286.1016, m/z 286.0985. Anal. Calcd for $C_{14}H_{16}O_4F_2$: C, 58.73; H, 5.63. Found: C, 58.67; H, 5.80.

(1*S*,3*S*,4*R*,5*S*)-4-[[(*p*-Tolylsulfonyl)oxy]methyl]-5-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (35). To the solution of 78 mg of alcohol **34** (0.29 mmol) in 2 mL of dry pyridine was added tosyl chloride (250 mg, 4 equiv). The mixture was allowed to stand overnight, and then 8 mL of ether was added. After filtration through a pad of Celite, the filtrate was evaporated to dryness. The crude tosylate was purified by flash chromatography (hexane/ethyl acetate, 10:1) to yield 90 mg of pure tosylate **35** (71% yield): $[\alpha]^{20}_D$ = +22.65° ($CHCl_3$, c = 1.13); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 and 7.50–7.17 (m, 9 H, 2 phenyls), 5.56 (m, 1 H, H-1), 4.84 (m, 1 H, H-3), 4.57 and 4.56 (d's, 2 H, CH_2-benzyl, J_{gem} = 12.0 Hz), 4.10 (dd, 1 H, H-8, J_{gem} = 10.5 Hz, $J_{8,4}$ = 4.4 Hz), 4.05 (m, 1 H, H-5), 4.03 (q, 1 H, H-8, J = 10.1 Hz), 3.63 (dd, 1 H, H-9, J_{gem} = 9.9 Hz, $J_{9,5}$ = 5.5 Hz), 3.53 (dd, 1 H, H-9′, J_{gem} = 9.9 Hz, $J_{9',5}$ = 5.6 Hz), 2.96 (m, 1 H, H-4), 2.47 (s, 3 H, SO_2CH_3); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 110.53 (d, $J_{F,F}$ = 193.3 Hz), 139.48 (dm, $J_{F,F}$ = 193.3 Hz); HRMS calcd for $C_{21}H_{22}O_6F_2S$ (M^+, 4) 440.1105, m/z 440.1113.

(1*S*,3*S*,4*R*,5*S*)-4-(Cyanomethyl)-5-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (36). A solution of tosylate **35** (28 mg, 0.064 mmol) in 2 mL of DMF and 100 mg of powdered dry sodium cyanide was stirred under nitrogen at 42 °C for 36 h. The mixture was then diluted with ether (5 mL) and filtered through a pad of Celite. The solvents were evaporated under a stream of nitrogen, and the DMF was evaporated in vacuo with addition of toluene. The crude product was purified by column chromatography (hexane/ethyl acetate 3:1) to yield 22 mg of pure nitrile **36**: $[\alpha]^{20}_D$ = +5.1° ($CHCl_3$, c = 2.05); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.30 (m, 5 H, phenyl), 5.62 (m, 1 H, H-1), 4.98 (m, 1 H, H-3), 4.62 and 4.60 (d's, 2 H, CH_2-benzyl, J_{gem} = 11.9 Hz), 4.12 (m, 1 H, H-5), 3.73 (dd, 1 H, H-9, J_{gem} = 9.8 Hz, $J_{9,5}$ = 5.0 Hz), 3.60 (dd, 1 H, H-9′, J_{gem} = 9.8 Hz, $J_{9',5}$ = 6.5 Hz), 2.95 (m, 1 H, H-4), 2.67 (dd, 1 H, H-8, J_{gem} = 17.2 Hz, $J_{8,4}$ = 5.3 Hz), 2.43 (dd, 1 H, H-8′, J_{gem} = 17.2 Hz, $J_{8',4}$ = 10.9 Hz); ^{19}F NMR ($CDCl_3$, 376.2

MHz) ϕ 103.35 (dd, $J_{F,F}$ = 192.6 Hz, $J_{H,F}$ = 3 Hz), 131.94 (dm, $J_{H,F}$ = 192.6 Hz); HRMS calcd for $C_{15}H_{15}NO_3F_2$ (M^+, 6) 295.1020, *m/z* 295.1017.

(1*S*,3*S*,4*R*,5*S*)-4-(Cyanomethyl)-5-(hydroxymethyl)-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (37). To a solution of nitrile **36** (73 mg, 0.247 mmol) in 3 mL of isopropyl alcohol was added 30 mg of 10% palladium on carbon, and the suspension was hydrogenated until the stoichiometric amount of hydrogen was consumed (the experiment had to be repeated three times). Passage through a pad of Celite and elution with ethyl acetate followed by evaporation of the solvents gave an oily substance, which was purified by column chromatography (hexane/ethyl acetate, 4:1, as eluant). Pure nitrile alcohol **37** (44 mg, 87%) was obtained as an oil: $[\alpha]^{22}_D$ = +26.4° ($CHCl_3$, *c* = 0.47); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.65 (m, 1 H, H-1), 4.96 (m, 1 H, H-3), 4.14 (m, 1 H, H-5), 3.89 (dm, 1 H, H-9, J_{gem} = 11.9 Hz), 3.76 (m, H-9), 3.12 (m, 1 H, H-4), 2.56 (dd, 1 H, H-8, J_{gem} = 17.1 Hz, $J_{8,4}$ = 6.8 Hz), 2.50 (dd, 1 H, H-8′, $J_{8',4}$ = 9.4 Hz), 1.99 (dd, 1 H, OH, $J_{9,OH}$ = 4.59, 7.53 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 103.82 (d, $J_{F,F}$ = 192.4 Hz), 132.35 (dm, $J_{F,F}$ = 192.4 Hz); HRMS calcd for $C_8H_9NO_3F_2$ (M^+ + 1, 4) 206.0628, *m/z* 206.0621. Anal. Calcd fr $C_8H_9F_2O_3N$: C, 46.83; H, 4.42. Found: C, 46.34; H, 4.43.

(1*S*,3*S*,4*R*,5*S*)-4-(Cyanomethyl)-5-(acetoxymethyl)-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (38). To a solution of nitrile alcohol **37** (6 mg, 0.029 mmol) in 40 μL of triethylamine (10 equiv) was added 9.4 μL of acetic anhydride (2.5 equiv), and the reaction mixture was stirred at 22 °C for 3 h. It was quenched with 1.0 mL of water and extracted with methylene chloride (3. × 2 mL). The methylene chloride extract was dried (Na_2SO_4) and concentrated, and the crude material was passed through a pipe column of silica gel, eluting with hexane/ethyl acetate (7:3). Pure acetate **38** (7.2 mg, 100%) was obtained as a colorless oil: $[\alpha]^{20}_D$ = +27.79° ($CHCl_3$, *c* = 0.34); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.56 (m, 1 H, H-1), 4.95 (m, 1 H, H-3), 4.35 (dd, 1 H, H-9, J_{gem} = 11.2 Hz, $J_{5,9}$ = 3.3 Hz), 4.25 (dd, 1 H, H-9′, J_{gem} = 11.7 Hz, $J_{5,9'}$ = 5.71 Hz), 4.22 (m, 1 H, H-5), 2.90 (m, 1 H, H-4), 2.59, 2.50 (two dd, 2 H, H-8, H-8′, J_{gem} = 17.1 Hz, $J_{4,8}$ = 10 Hz, $J_{4,8'}$ = 6.1 Hz), 2.15 (s, 3 H, OAc); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 103.40 (d, $J_{F,F}$ = 192.6 Hz), 132.24 (dt, $J_{F,F}$ = 193.0 Hz, $J_{H,F}$ = 5.5 Hz).

(1*S*,3*S*,4*R*,5*S*)-4-(2-Oxyethyl)-5-(hydroxymethyl)-7,7-difluoro-2,6-dioxabicyclo[3.1.1]heptane (39). The nitrile **37** (18.5 mg, 0.0748 mmol) in 1.8 mL of CH_2Cl_2 was cooled to −26 °C (dry ice/CCl_4 bath), and 1.0 M DIBAL-H in hexane (150 μL, 0.150 mmol) was slowly added dropwise. The mixture was stirred at −26 °C for 2 h and then quenched with 1.5 mL of saturated NH_4Cl and several drops of 0.1 N HCl solution until the aqueous layer became clear (pH 3.5). The solution was then extracted with CH_2Cl_2 (10 × 2 mL), and the CH_2Cl_2 extract was dried (Na_2SO_4) and then filtered through a Celite pipet column. The filtrate was evaporated at −10 °C by a slow stream of nitrogen. The resulting aldehyde **39** (12.2 mg, 78.3%) was used without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.73 (s, 1 H, C*H*O), 5.65 (m, 1 H, H-1), 4.87 (m, 1 H, H-3), 4.10 (m, 1 H, H-5), 3.80 (m, 1 H, H-9), 3.68 (m, 1 H, H-9′), 3.28 (m, 1 H, H-4), 2.70 and 2.66 (dd's, 1 H each, H-8, H-8′, J_{gem} = 18.8 Hz, $J_{4,8}$ = 8.7 Hz, $J_{4,8'}$ = 5.5 Hz), 2.03 (t, 1 H, OH, *J* = 6.4 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 104.19 (dd, $J_{F,F}$ = 190.7 Hz, $J_{H,F}$ = 3.1 Hz), 132.28 (dt, $J_{F,F}$ = 191.4 Hz, $J_{H,F}$ = 6.2 Hz).

10,10-Difluoro-13-hydroxy-9β,11β-14,15,16,17,18,19,20-heptanorthromboxane A_2 Methyl Ester (40) and Its 5,6-*E* Isomer (41). To a stirred solution of (4-carboxybutyl)triphenylphosphonium bromide (109 mg, 0.246 mmol) in 0.6 mL of dry THF at 0 °C was added 542 μL of 1.0 M $LiN(TMS)_2$ in THF (0.542 mmol), and the mixture was stirred for 30 min at 0 °C. At this time the aldehyde **39** (12.2 mg, 0.058 mmol in 100 μL of THF) was added, and stirring was continued for 30 min at 0 °C and then at room temperature for 3 h. The mixture was then quenched with 3.0 mL of saturated aqueous NH_4Cl solution, and THF was removed by a stream of dry nitrogen. The mixture was carefully acidified to pH 3.50 with 0.1 N HCl, extracted with ethyl acetate (10 × 5 mL), dried (Na_2SO_4), and evaporated. The residue was dissolved in 1.0 mL of EtOEt/CH_3OH (4:1) and methylated with ethereal diazomethane at 0 °C. Removal of the solvent under nitrogen and flash chromatography of the residue gave a mixture of cis and trans esters: HRMS calcd for $C_{13}H_{17}O_4F_2$ ($M - OCH_3$, 8) 275.1095, *m/z* 275.1106. Anal. Calcd for $C_{14}H_{20}O_4F_2$: C, 54.89; H, 6.58. Found: C, 53.27; H, 6.51.

This material was further purified by normal-phase HPLC (silica gel column) using hexane:CH_2Cl_2:EtOAc = 10:10:3 as eluant (3 mL/min, 6-mL fractions). The faster moving component, collected at 36–42 min, was the 5-cis product **40**. The slower moving one, collected at 46–50 min, was the 5-trans product **41**. Total yield (cis + trans) was 11.5 mg (65%). The ratio of cis/trans was 3.25:1 as determined by ^{19}F NMR integration.

40: $[\alpha]^{20}_D$ = +29.14° (*c* = 0.35 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.60 (m, 1 H, H-11), 5.52 (m, 1 H, H-5), 5.37 (m, 1 H, H-6), 4.75 (m, 1 H, H-9), 4.12 (m, 1 H, H-12), 3.83 (m, 1 H, H-13), 3.68 (s, 3 H, OCH_3), 3.63 (m, 1 H, H-13′), 2.65 (m, 1 H, H-8), 2.33 (t, 2 H, H-2, *J* = 7.4 Hz), 2.25–2.03 (m, 5 H, H-4, H-7, OH), 1.72 (p, 2 H, H-3, *J* = 7.4 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 104.03 (dd, $J_{F,F}$ = 189.9 Hz, $J_{H,F}$ = 2.4 Hz), 131.77 (dt, $J_{F,F}$ = 189.9 Hz, $J_{H,F}$ = 6.2 Hz).

41: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.61 (m, 1 H, H-11), 5.50 (m, 1 H, H-5), 5.34 (m, 1 H, H-6), 4.78 (m, 1 H, H-9), 4.10 (m, 1 H, H-12), 3.82 (m, 1 H, H-13), 3.68 (s, 3 H, OCH_3), 3.61 (m, 1 H, H-13′), 2.67 (m, 1 H, H-8), 2.32 (t, 2 H, H-2, *J* = 7.4 Hz), 2.15 (m, 2 H, H-7), 2.07 (q, 2 H, H-4, $J_{3,4}$ = $J_{4,5}$ = 6.8 Hz), 2.02 (dd, 1 H, OH *J* = 7.6, 5.6 Hz), 1.72 (p, 2 H, H-3, *J* = 7.4 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 103.91 (dd, $J_{F,F}$ = 189.9 Hz, $J_{H,F}$ = 2.2 Hz), 131.77 (dt, $J_{F,F}$ = 189.9 Hz, $J_{H,F}$ = 6.2 Hz). When NaN $(TMS)_2$ was substituted for the lithium salt, the cis/trans ratio was changed to 4:1.

10,10-Difluoro-13-oxo-9β,11β-14,15,16,17,18,19,20-heptanorthromboxane A_2 Methyl Ester (42). To a solution of oxalyl chloride (3.72 mg, 0.0294 mmol) in 30 μL of dry CH_2Cl_2 at −78 °C was added DMSO dropwise (4.56 mg, 0.0588 mmol in 30 μL of dry CH_2Cl_2) with stirring. After 15 min, the cis alcohol **50** (6.0 mg, 0.0196 mmol) in 100 μL of dry CH_2Cl_2 was added. The mixture was stirred at −78 °C for 5 min, and triethylamine (25 μL, 0.179 mmol) was added. After stirring for an additional 5 min, it was quenched with 1.0 mL of water and extracted with CH_2Cl_2 (10 × 1 mL). The CH_2Cl_2 extract was dried (Na_2SO_4), filtered, and concentrated under a slow stream of N_2 at −10 °C. The resulting residue was passed through a silica gel pipet column eluting with EtOAc/hexane, 1:4. The resulting aldehyde **42** was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.70 (s, 1 H, CHO), 5.70 (m, 1 H, H-11), 5.52 (m, 1 H, H-5), 5.37 (m, 1 H, H-6), 4.83 (m, 1 H, H-9), 4.27 (dd, 1 H, H-12, $J_{8,12}$ = 7.3 Hz, $J_{12,13}$ = 2.3 Hz), 3.68 (s, 3 H, OCH_3), 2.82 (m, 1 H, H-8), 2.33 (t, 2 H, H-2, *J* = 7.3 Hz), 2.10 (m, 4 H, H-4, H-7), 1.72 (p, 2 H, H-3, *J* = 7.4 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 104.45 (d, $J_{F,F}$ = 190.6 Hz), 131.69 (dt, $J_{F,F}$ = 190.6 Hz, $J_{H,F}$ = 3.1 Hz).

10,10-Difluoro-9β,11β-15-oxothromboxane A_2 Methyl Ester (43). A solution of dimethyl (2-oxoheptyl)phosphonate (8.8 mg, 0.04 mmol) in 200 μL of dry THF was cooled to 0 °C (ice bath). To this solution was added 40 μL (0.04 mmol) of 1.0 M $LiN(TMS)_2$ in THF with stirring. After 10 min, a solution of the aldehyde **42** obtained in the previous experiment was added in 100 μL of THF. The reaction mixture was stirred at 22 °C for 3 h and was then quenched with 1.0 mL of water. Extraction with CH_2Cl_2 (10 × 1 mL), drying (Na_2SO_4), and evaporation gave crude **43**, which was purified by elution on a short pipet silica gel column using 20% EtOAc/hexane (1:4) as eluant to yield 5.2 mg of **43** (66% from alcohol **40**): $[\alpha]^{20}_D$ = +28.15° (*c* = 0.38 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.78 (dd, 1 H, H-13, $J_{13,14}$ = 15.7 Hz, $J_{12,13}$ = 5.7 Hz), 6.38 (dd, 1 H, H-14, $J_{13,14}$ = 15.7 Hz, $J_{12,14}$ = 1.03 Hz), 5.65 (m, 1 H, H-11), 5.55 (m, 1 H, H-5), 5.33 (m, 1 H, H-6), 4.78 (m, 1 H, H-9), 4.58 (m, 1 H, H-12), 3.68 (s, 3 H, OCH_3), 2.59 (t, 2 H, H-16, *J* = 7.4 Hz), 2.50 (m, 1 H, H-8), 2.34 (t, 2 H, H-2, *J* = 7.4 Hz), 2.25 (m, 1 H, H-7), 2.16 (m, 1 H, H-7′), 2.08 (m, 2 H, H-4), 1.73 (p, 2 H, H-3, *J* = 7.4 Hz), 1.65 (p, 2 H, H-17, *J* = 7.4 Hz), 1.33 (m, 4 H, H-18, H-19), 0.92 (t, 3 H, H-20, *J* = 6.4 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 102.76 (d, $J_{F,F}$ = 190.8 Hz), 131.07 (dt, $J_{F,F}$ = 190.7 Hz, $J_{H,F}$ = 9.2 Hz).

10,10-Difluoro-9β,11β-thromboxane A_2 Methyl Ester (44) and Its 15*R* Isomer (45). To a stirred solution of **43** (5 mg) in 500 μL of 0.4 M $CeCl_3 \cdot 7H_2O$ (prepared from 149 mg of $CeCl_3 \cdot 7H_2O$ in 1 mL of methanol) was added $NaBH_4$ (10 mg). The mixture was allowed to stir for 5 min and was then quenched with 1 mL of water and extracted with ethyl ether (10 × 1 mL). The ether extract was dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (pipet column) using EtOAc/hexane (1:4) as eluant: yield, 4.0 mg (80%) (**44**:**45** = 1:1); HRMS (isobutane) calcd for $C_{21}H_{32}O_5F_2$ (M + 1, 28) 403.2296, *m/z* 40.2326. This was further purified by normal-phase HPLC chromatography (silica gel, 10 mm i.d. column) 1% *n*-PrOH/99% hexane as eluant at 3 mL/min detected at 205 nm to give pure 15*R* (**45**) at 25–26 min and pure 15*S* (**44**) at 29–30 min.

44: $[\alpha]^{20}_D$ = +28.66° (*c* = 0.15 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.82 (dd, 1 H, H-14, $J_{13,14}$ = 15.6 Hz, $J_{14,15}$ = 5.8 Hz), 5.72 (dd, 1 H, H-13, $J_{13,14}$ = 15.6 Hz, $J_{12,13}$ = 7.8 Hz), 5.60 (m, 1 H, H-11), 5.48 (m, 1 H, H-5), 5.32 (m, 1 H, H-6), 4.73 (m, 1 H, H-9), 4.40 (m, 1 H, H-12), 4.15 (m, 1 H, H-15), 3.68 (s, 3 H, OCH_3), 2.40 (m, 1 H, H-8), 2.32 (t, 2 H, H-2, *J* = 7.6 Hz), 2.18–2.0 (m, 4 H, H-4, H-7), 1.70 (p, 2 H, H-3, *J* = 7.3 Hz), 1.60–1.20 (m, 8 H, H-16, H-17, H-18, H-19), 0.89 (t, 3 H, H-20, *J* = 6.80 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 102.41 (dm, $J_{F,F}$ = 191.2 Hz), 130.57 (dm, $J_{F,F}$ = 191.2 Hz).

45: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (dd, 1 H, H-14, $J_{13,14}$ = 15.4 Hz, $J_{14,15}$ = 5.7 Hz), 5.72 (dd, 1 H, H-13, $J_{13,14}$ = 15.4 Hz, $J_{12,13}$ = 7.8 Hz), 5.58 (m, 1 H, H-11), 5.48 (m, 1 H, H-5), 5.35 (m, 1 H, H-6), 4.75 (m, 1 H, H-9), 4.39 (m, 1 H, H-12), 4.17 (m, 1 H, H-15), 3.68 (s, 3 H,

OCH_3), 2.39 (m, 1 H, H-8), 2.30 (dt, 2 H, H-2, J = 7.3 Hz, J = 1.8 Hz), 2.10 (t, 2 H, H-4, J = 7.8 Hz), 2.05 (t, 2 H, H-7, J = 7.8 Hz), 1.68 (dp, 2 H, H-3, J = 7.3 Hz, J = 1.5 Hz), 1.60–1.20 (m, 8 H, H-16, H-17, H-18, H-9), 0.9 (t, 3 H, H-20, J = 6.9 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 102.37 (d, $J_{F,F}$ = 192.6 Hz), 130.49 (dm, $J_{F,F}$ = 192.6 Hz).

10,10-Difluoro-9β,11β-thromboxane A_2 Methyl Ester (44). A THF solution of the reducing agent S-1 was prepared by treating $LiAlH_4$ in THF (1.0 M solution in THF) with equimolar amounts of ethanol (1.0 M solution in THF) and optically pure (*S*)-(−)-1,1′-bi-2-naphthol (0.5 M solution in THF) at 0 °C and then stirring at 22 °C for 1 h. Three equivalents of the freshly prepared reducing agent (S-1) (7.5 μmol) was cooled at −78 °C, and to this cold cloudy mixture was added the α,β-unsaturated ketone **43** (1.0 mg, 2.5 μmol, in 100 μL of dry THF). The mixture was stirred at −78 °C for 3 h and then quenched with moist ethyl ether, filtered through a Celite pipet column, and concentrated. Crystallization from hexane with a trace of ethyl ether gave recovered chiral auxillary ligand, (*S*)-(−)-1,1′-bi-2-naphthol. Normal-phase HPLC chromatography of the residue (silica gel, 10 mm i.d. column) with 1% *n*-PrOH/99% hexane as eluant (3 mL/min, detected at 205 nm) gave pure the 15*S* isomer (**44**, 0.6 mg) at 29, 30, and 31 min. This material was found to be identical by ^{1}H and ^{19}F NMR with the slower moving isomer obtained in the $NaBH_4$ reduction.

10,10-Difluoro-9β,11β-thromboxane A_2 (46). To a solution of the methyl ester of 10,10-difluorothromboxane (≈300 μg) in 250 μL of methanol was added 250 μL of 1 N NaOH. The mixture was stirred at 22 °C for 1 h and carefully acidified with 0.1 N HCl to pH 3, and the hydrolysate was extracted with ethyl acetate (10 × 1 mL). The ethyl acetate extract was dried (Na_2SO_4), filtered, and concentrated to give **46** (205 μg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.88 (dd, 1 H, H-14, $J_{13,14}$ = 15.5 Hz, $J_{14,15}$ = 5.0 Hz), 5.77 (dd, 1 H, H-13, $J_{13,14}$ = 15.5 Hz, $J_{12,13}$ = 7.0 Hz), 5.60 (m, 1 H, H-11), 5.47 (m, 1 H, H-5), 5.43 (m, 1 H, H-6), 4.82 (m, 1 H, H-9), 4.40 (m, 1 H, H-12), 4.29 (m, 1 H, H-15), 2.40 (m, 1 H, H-8), 2.32 (m, 2 H, H-2), 2.20 (m, 2 H, H-4), 2.0 (m, 4 H, H-7, H-3), 1.80–1.20 (m, 8 H, H-16, H-17, H-18, H-19), 0.90 (t, 3 H, H-20, J = 6.5 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 102.37 (d, $J_{F,F}$ = 190.7 Hz), 130.34 (d, $J_{F,F}$ = 190.7 Hz).

(15*R*)-10,10-Difluoro-9β,11β-thromboxane A_2 (46A). Following the procedure for the preparation of the 15*S* isomer, the 15*R* isomer **46A** was obtained: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.80 (dd, 1 H, H-14, $J_{13,14}$ = 15.3 Hz, $J_{14,15}$ = 6.5 Hz), 5.73 (dd, 1 H, H-13, $J_{13,14}$ = 15.3 Hz, $J_{12,13}$ = 7.7 Hz), 5.58 (m, 1 H, H-11), 5.48 (m, 1 H, H-5), 5.43 (m, 1 H, H-6), 4.83 (m, 1 H, H-9), 4.36 (m, 1 H, H-12), 4.30 (t, 1 H, H-15, J = 6.5 Hz), 2.35 (m, 4 H, H-8, H-2), 2.15 (m, 2 H, H-4), 2.03 (m, 4 H, H-3, H-7), 1.80–1.20 (m, 8 H, H-16, H-17, H-18, H-19), 0.89 (t, 3 H, H-20, J = 6.3 Hz); ^{19}F NMR ($CDCl_3$, 376.2 MHz) ϕ 102.32 (dd, $J_{F,F}$ = 191 Hz, $J_{H,F}$ = 3.1 Hz), 130.20 (dt, $J_{F,F}$ = 191 Hz).

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Structure and Chemical Properties of Ptilomycalin A

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Abstract: The structure of ptilomycalin A (**1**), a marine alkaloid possessing potent antiviral and antibiotic activites, has been determined on the basis of NMR analyses of its trifluoroacetyl (TFA) derivative (**2**). It has a unique structure consisting of a polycyclic guanidine and a spermidine group, each of which is linked to a 16-hydroxyhexadecanoic acid moiety. The rotational isomerism of the acylated sperimidine moiety of **2** has been studied by comparing the NMR properties of the synthetic trifluoroacetyl derivatives of spermidine (**5**), dipropylenetriamine (**11**), diethylenetriamine (**12**), and pentylamine (**13**). From these experiments, a plausible conformation of **2** and ptilomycalin A (**1**) has been proposed as shown in **2c**, in which an anion is trapped between the guanidine and spermidine moieties. The TFA derivative **2** acts as a phase-transfer agent. NMR analysis of the stability of the complexes formed between **2** and several organic carboxylates in $CDCl_3$ solutions has been carried out.

Introduction

A large number of studies on marine natural products have been carried out in the past two decades, firstly because marine organisms produce pharmaceutically and biologically important substances[1] and secondly because many marine natural products possess unusual chemical structures that are seldom found in the metabolites of terrestrial organisms.[2] Examples are polycyclic ethers such as palytoxin,[3] brevetoxins,[4] okadaic acid,[5] and ciguatoxin.[6] They are of physiological importance and have unique and complex structures.

It should be noted that relatively few alkaloids have been found from marine resources,[7] while a large number of alkaloids have been isolated from terrestrial plants, many of which have been used for a long time as drugs to cure human diseases.

In the course of screening for novel bioactive agents from marine sponges, we have isolated an antitumor, antiviral, and antifungal compound designated ptilomycalin A (**1**) from the Caribbean sponge *Ptilocaulis spiculifer*.[8] The same compound was also isolated from a Red Sea sponge of *Hemimycale* sp. Ptilomycalin A shows cytotoxicity against P388 (IC_{50} 0.1 μg/mL), L1210 (IC_{50} 0.4 μg/mL), and KB (IC_{50} 1.3 μg/mL) and antifungal activity against *Candida albicans* (MIC 0.8 μg/mL) as well as very good

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