Synthesis of a Thromboxane A_2 Receptor Antagonist Possessing the Dioxabicycloheptane Nucleus of TXA_2

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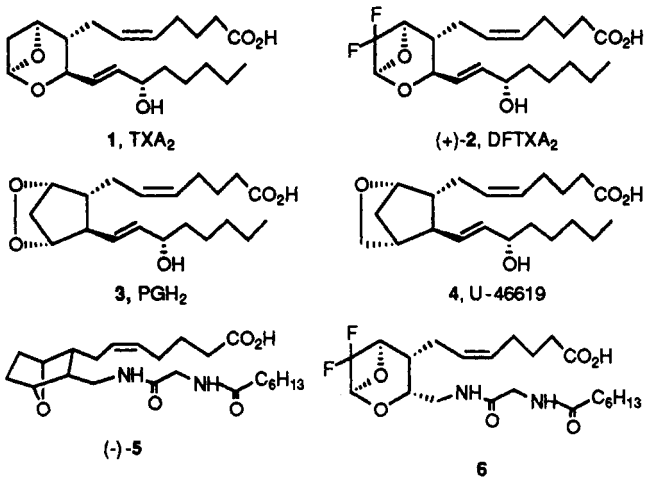
The synthesis of the TXA_2/PGH_2 receptor antagonist **6** from the known chiral intermediate (−)-**8** is described. The critical reaction is the inversion of C-5 in **11a** and **11b** by an intramolecular cyclization reaction induced by nucleophilic reagents as shown in structure **13a**. The key intermediate **22** was prepared in 26.5% yield in five steps. Diastereoselectivity is high in all but one of the steps, the Reformatsky reaction, which leads to equal amounts of **11a** and **11b**. The design of **6** is based on the dioxabicycloheptane nucleus characteristic of TXA_2 (**1**), which has been stabilized by fluorination. To this nucleus the two side chains are attached in cis orientation, and the ω-chain is modified as reported for the receptor antagonist (−)-**5**, which in turn is an analogue of PGH_2 (**3**). These changes in the side chains have the effect of converting the powerful agonist **2** ($DFTXA_2$) into a receptor antagonist devoid of agonist activity, which binds to the receptor with nanomolar affinity. These findings lend support to the view of a single TXA_2/PGH_2 receptor.

Introduction

Thromboxane A_2 (TXA_2, **1**), 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 diseases.[2-6] It is unique among eicosanoids because of its oxetane acetal 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 recently been described.[8] Because of its unusual lability at physiological pH there has been much interest in synthesizing stable analogues of this eicosanoid in order to mimic its biological properties, inhibit its biosynthesis, or block the actions of TXA_2 (**1**) at the receptor level.[9a,b] The efforts by this laboratory to achieve increased stability by fluorination of the dioxabicyclo[3.1.1]heptane nucleus resulted in the synthesis of 10,10-difluorothromboxane A_2 ($DFTXA_2$, **2**),[10,11] a compound which not only possessed greater chemical stability than predicted but also retained and even exceeded the biological activity of natural TXA_2.[12] This work provided evidence that fluorine did not interfere with receptor binding but, on the contrary, served to increase it. Our original intention for carrying out this work, namely to demonstrate the biochemical equivalence of the TXA_2 nucleus and that of its difluoro derivative **2**, was therefore answered in the affirmative.



The stage was thus set to construct a receptor antagonist, based on the difluorodioxabicyclo[2.2.1]heptane nucleus present in **2**, most expeditiously by modification of one or both of the side chains. Among the voluminous literature on the subject of TXA_2 receptor antagonists[9] a paper by Nakane et al.[13] caught our attention. It describes a series of potent and selective antagonists based on the 7-oxabicyclo[2.2.1]heptane nucleus, in which the two side chains are cis-α-oriented and the ω-chain is significantly modified. The authors selected (−)-**5** as the most effective representative of this class of compounds for clinical trials. The oxabicycloheptane nucleus present in (−)-**5** is an analog

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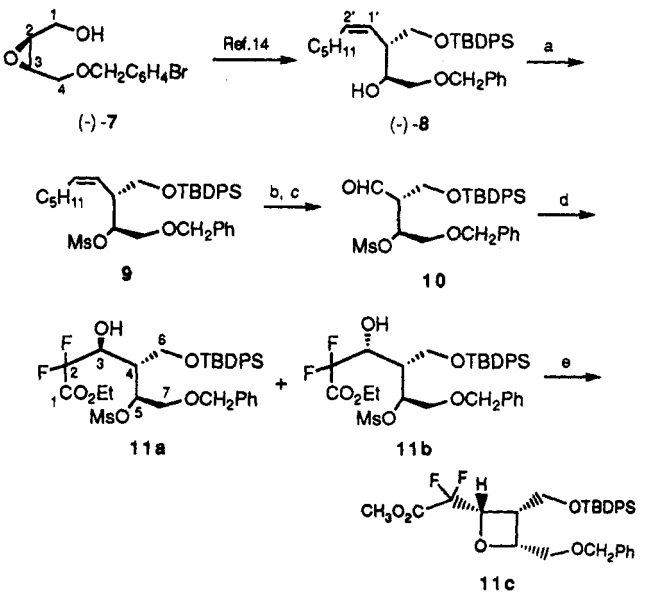
of the dioxabicycloheptane nucleus present in PGH_2 (3). All presently available evidence indicates that both PGH_2 and TXA_2 are ligands for the same receptor, which is therefore referred to as the TXA_2/PGH_2 receptor. On the basis of this premise combining the difluoro-TXA_2 nucleus with the cis-oriented side chains of (−)-5 as represented by 6 should produce a powerful TXA_2/PGH_2 receptor antagonist. It would serve to test the concept of whether predictable biological results can be realized by combining the structural features promoting receptor binding established with a TXA_2 agonist with those effective in blocking the agonist response of an analog of PGH_2. Here, the synthesis of the hybrid structure 6 is described together with its biological characterization as a selective receptor antagonist devoid of TXA_2 agonist activity.

Synthesis

The synthesis of 6 leans heavily in its strategy on our recently reported synthesis of DFTXA$_2$, 2,[14] starting from the chiral Sharpless epoxidation product (−)-7.[15] It was beset, however, with significant problems caused by the presence of the cis-oriented side chains. The original plan to effect an inversion at C-3 of the intermediate 9 failed because of facile elimination of methanesulfonic acid, so it became necessary to modify this strategy. In spite of this the mesylate 9 turned out to be an appropriate intermediate. Cleavage of the alkenyl side chain with ozone in CH_2Cl_2 in the presence of 1.5 equiv of MeOH[14] furnished the crude aldehyde 10 in quantitative yield, which on attempted purification on silica gel suffered elimination faster than anticipated. The crude aldehyde and residual hexanal were therefore used for the Reformatsky reaction with ethyl bromodifluoroacetate.[14,16] The yield of the isomeric hydroxy esters 11a and 11b, formed in a 1:1 ratio, was excellent (95%) (Scheme I). The initial assignment of the newly generated C-3 hydroxyl group was based on precedent,[14,17] the more polar product being assigned the α-configuration (11b). Attempted correlation of these isomers with those of known configuration such as disilyl ether 12[14] was unsuccessful as all attempts to effect selective desilylation at C-5[18] resulted in formation of the lactone 12a, instead of the alcohol ester (Scheme II). Opening of 12a with Na/EtOH was accompanied by acetyl migration (O-3 to O-5) as shown in Scheme II. Mesylation of the resulting hydroxy ester gave 12c, rather than the expected 3-acetate of 11b. Conclusive evidence for the configuration at C-3 was later effected by proton NMR which confirmed our original assignments (vide infra).

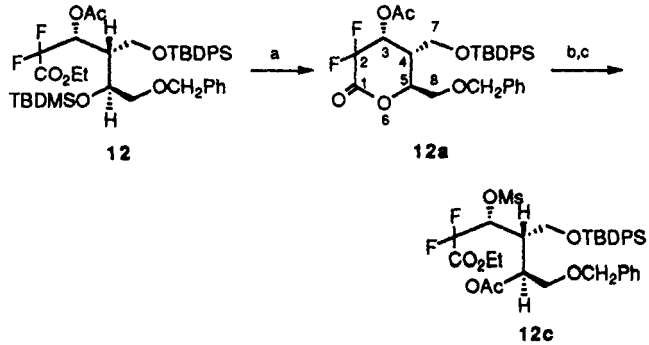
Our aim at this stage was to invert the center at C-5 of 11a and 11b via an intramolecular S_N2 reaction by an anion generated at C-1. Reaction of 11b with K_2CO_3 in MeOH/H_2O (4:1) led, however, to the oxetane 11c by attack of the 3-oxy anion at C-5. This reaction is not entirely unexpected since the increased acidity of the 3-hydroxyl group due to neighboring CF_2 would result in a significant 3-oxy anion concentration, resulting in irreversible oxetane formation. On the basis of this finding it was reasoned

Scheme I[a]



[a] Conditions: (a) MsCl/py; (b) O_3; (c) Me_2S; (d) $BrCF_2CO_2Et$, Zn, THF, 0–10 °C; (e) K_2CO_3/80% aqueous MeOH.

Scheme II[a]



[a] Conditions: (a) AcOH/H_2O, 65 °C; (b) Na/EtOH, 19 °C; (c) MsCl/py.

that a weaker basic nucleophile in a non-nucleophilic medium would fail to abstract the 3-hydroxyl proton and result in nucleophilic addition to the 1-carbethoxy group,[19] giving rise to the intermediate anion 13a, which in an intramolecular S_N2 reaction would, hopefully, lead to 13b with inversion at C-5. The latter would be expected to collapse to 14 either spontaneously or on treatment with acid. Such an interpretation of the anticipated mechanism is shown in Scheme III. When 11b was refluxed with CsOAc in DME, a product was formed whose proton and fluorine signals were broad and no longer showed the presence of mesylate. When the material was treated with dilute HCl, workup with ether furnished the desired lactone, 14. That the oxy anion 13a is indeed the intermediate in this replacement reaction was affirmed by substituting iodide or cyanide for acetate, both of which furnished the lactone in excellent yield. Similarly, 11a reacted to give the corresponding lactone 15.

There remained the unambiguous assignment of the stereochemistry at C-3 for the two epimers. For this purpose acetates 14a and 15a were prepared from the corresponding lactones. The two possible half-chair conformations of each of the two epimers are shown in Scheme IV. Of the alternative conformations for the α-epimer, 14a$_1$ should be the preferred one, while 15a$_2$

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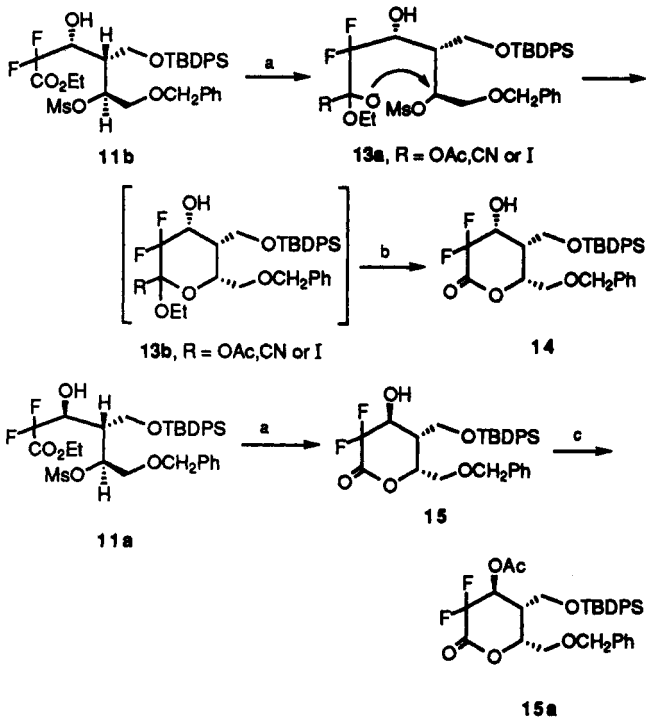
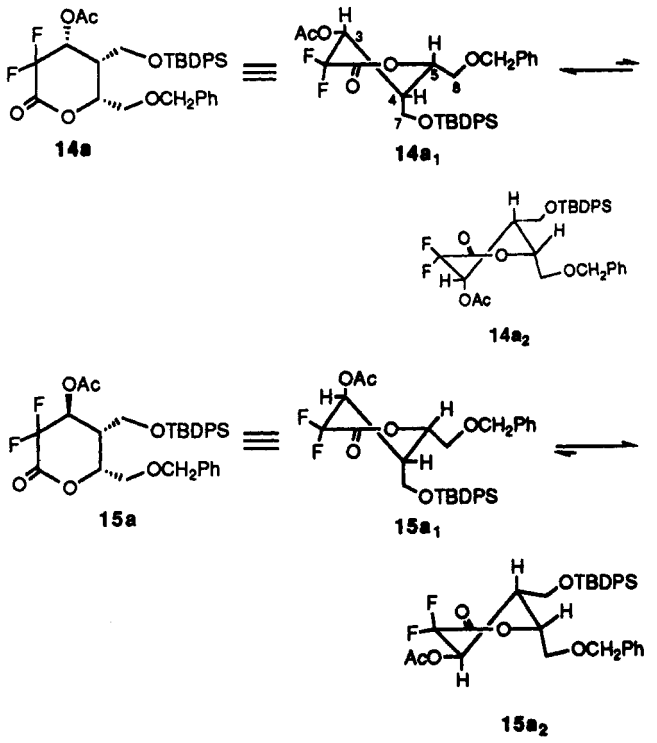
Scheme III[a]



[a] Conditions: (a) CsOAc/DME/90 °C; (b) 2 N HCl; (c) Ac_2O/py.

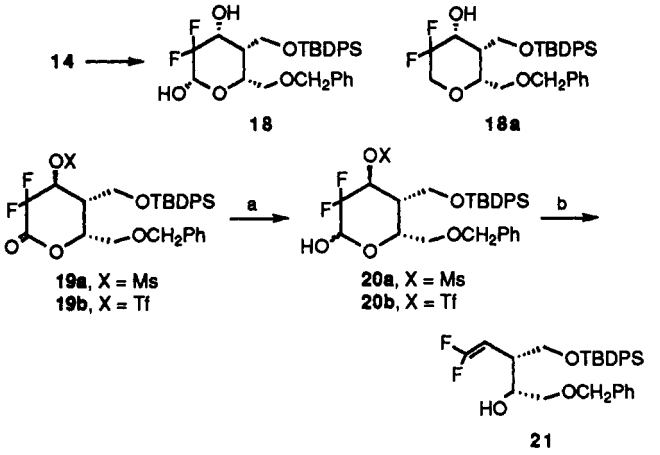
Scheme IV



should represent the preferred conformation for the β-epimer. The coupling constants for the C-3 proton in the two acetates derived from double irradiation experiments proved decisive in making the assignment shown in structures **14a** and **15a**.

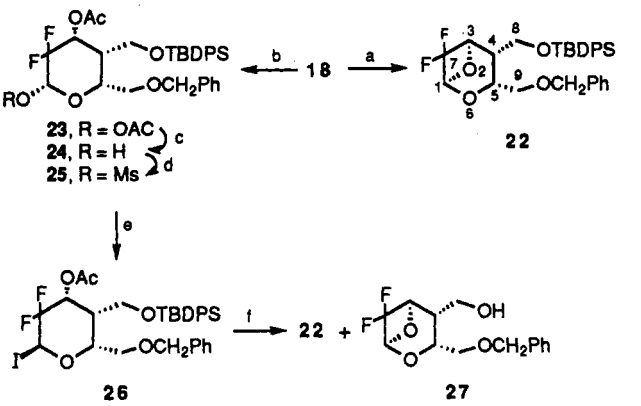
The spectrum of the 3β-acetate **15a** showed C-3H as an eight-line pattern at δ 5.92 with a large coupling to fluorine (J = 16.2 Hz) and trans-diaxial coupling to C-4H (J = 11.2 Hz), in line with conformation **15a₂**. In the case of the 3α-acetate **14a**, C-3H had a clear trans-diaxial H–F

Scheme V[a]



[a] Conditions: (a) $NaBH_4$/MeOH, −40 °C; (b) LHMDS/HMPA, 60 °C.

Scheme VI[a]



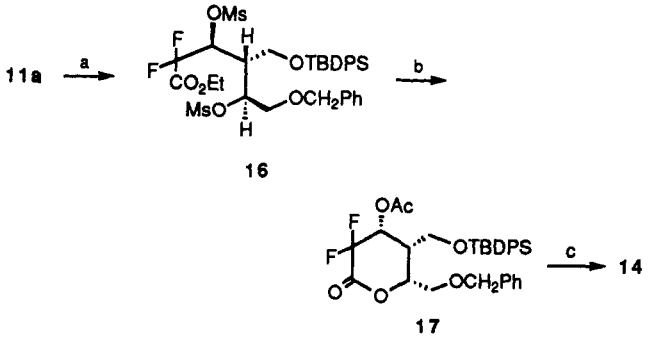
[a] Conditions: (a) PPh_3/DEAD; (b) Ac_2O/py; (c) $NaHCO_3$/MeOH/H_2O; (d) MsCl/py; (e) NaI/DMF, 50 °C; (f) K_2CO_3/MeOH/H_2O.

coupling (19.9 Hz) and a small coupling (J = 4.7 Hz) to C-4H as anticipated for **14a₁**. The signals for C-4H for **14a** and **15a** appeared at δ = 2.45 and 2.75, respectively, and those for C-5H at δ = 5.45 and 4.86, respectively, supporting conformations **14a₁** and **15a₂** as the more stable ones for **14a** and **15a**.

With the stereochemistry at C-3 now secure it was possible to proceed to the next step of the synthesis, formation of the bicyclic oxetane. Reduction of the lactone **14** with $NaBH_4$ (2 equiv) in MeOH at −40 °C for 20 min proceeded as expected to give the lactol **18** in 60% yield after purification (Scheme V). Reduction at higher temperature/excess $NaBH_4$ led to tetrahydropyran **18a** as a byproduct. All attempts to effect oxetane formation following the methodology developed for the synthesis of the 4,5-trans-substituted oxetanes[14] failed when applied to either **18** or its 3β-epimer (Scheme V). Thus, mesylation of **18** yielded only the 1α,3α-dimesylate rather than the desired 1β-mesylate. The alternative of reducing the 3α-acetoxy lactone likewise failed because of its resistance to borohydride or DIBAL-H reduction. Similarly, attempts to cyclize the 3β-mesylate **20a** or the triflate **20b** with LHMDS/HMPA, successful in the trans series,[14] led only to equilibration at C-1 in the case of the mesylate **20a** and to fragmentation to **21** in the case of the triflate.

Successful cyclization of **18** to the target oxetane **22** was achieved using the Mitsunobu reaction (Scheme VI) according to Still et al.[8] This alternative had been avoided

Scheme VII[a]



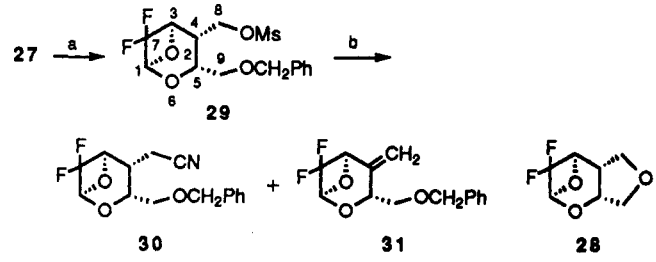
[a] Conditions: (a) MsCl/py; (b) CsOAc/DME, 90 °C (c) K_2CO_3/MeOH/H_2O.

because of the poor yields (18%)[8] generally obtained in such cyclization reactions.[20] However, it was possible to increase the yield to 47% using PPh_3 and freshly distilled DEAD. The resulting oxetane **22** was believed to possess the α-oxide bridge based on the fact that the starting lactol **18** had the 3α-configuration and on the assumption that introduction of the leaving group takes place at C-1 rather than at C-3. Such an assumption is, however, not warranted since no preference was observed in the acylation and mesylation reactions of **18**. We felt it necessary, therefore, to provide unambiguous evidence for the structure of **22**. This was accomplished in the following way (Scheme VI): The diacetate **23** was selectively hydrolyzed with $NaHCO_3$/MeOH/H_2O to give the 3α-monoacetate **24**, which on mesylation afforded the 1α-mesylate, **25** ($J_{H1,F}$ = 7.5 Hz). The latter on reaction with NaI/DMF at 50 °C yielded 1β-iodo ether **26** ($J_{H1,F}$ = 12.4 Hz), which was unusually stable permitting chromatographic purification on SiO_2. The C-1 and C-3 substituents now possess suitable stereochemistry to undergo α-oxetane formation. Indeed, treatment of **26** with K_2CO_3/MeOH/H_2O gave the expected oxetane **22** identical with that obtained from the Mitsunobu reaction. In addition to **22**, the desilylated product **27** was formed in 20% yield. The overall yield starting from lactol **18** by the above method was 20%.

In order to utilize the 3β-Reformatsky ester **11a** for the preparation of the α-oxetane, it was converted to the dimesylate **16**, which on treatment with CsOAc suffered inversion at C-3 and C-5 furnishing the 3α-acetate lactone **17** in quantitative yield (Scheme VII). Hydrolysis of **17** yielded the 3α-hydroxy lactone **14** after workup with acid. Desilylation of **22** with tetrabutylammonium fluoride afforded the oxetane **27** in 89% yield.

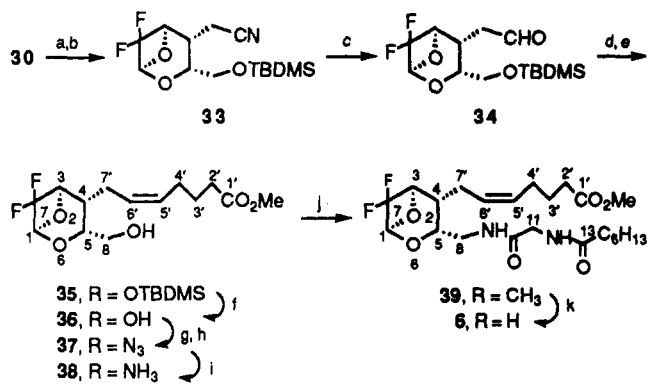
Tosylation of **27** was very slow and furnished in addition to the desired tosylate the tetrahydrofuran **28** (Scheme VIII). This product became the exclusive product on attempted triflation. The formation of **28** in these reactions is undoubtedly due to attack of the cis-oriented benzyl ether oxygen on the C-8 methylene group to form an oxonium salt which readily loses the benzyl group with the available counterions. On the other hand, mesylation of **27** occurred rapidly and cleanly to yield **29** in 94% yield. Complications due to the cis-oriented side chains continued to cause problems in the next step, the preparation of the nitrile **30** from **29**. Following the conditions established

Scheme VIII[a]



[a] Conditions: (a) MsCl/py, 0 °C; (b) NaCN/DMF, 30 °C.

Scheme IX[a]



[a] Conditions: (a) H_2/Pd/C,Me_2CHOH; (b) TBDMSCl,NEt_3,DMAP; (c) DIBALH; (d) $BrPh_3P(CH_2)_4CO_2H$,$NaN(TMS)_2$; (e) CH_2N_2; (f) Bu_4NF; (g) $(TfO)_2O$,py; (h) NaN_3/DMF; (i) PPh_3/THF/H_2O; (j) $C_6H_{13}CONHCH_2CO_2H$, 1,1′-dicarbonyldiimidazole; (k) 0.3 N NaOH.

in the trans series,[14] the major products were **28** and the elimination product **31**. Decreasing the basicity of the reaction medium by reducing the excess of cyanide from 10 to 2 equiv and lowering the temperature of the reaction reduced the amount of both **31** and **28**. These modified reaction conditions increased the yield of **30** to 75% at 36% conversion of **29**. The recovered mesylate was recycled. Debenzylation of **30** was effected using 10% Pd on carbon in dry 2-propanol to give the nitrile alcohol **32** in 94% yield.

In order to extend the upper side chain we had previously employed the reduction of the cyano alcohol with DIBAL-H.[14] This reaction when applied to the *cis*-cyano alcohol **32** afforded an unbreakable and unidentifiable aluminum complex. Protection of the alcohol as the TBDMS ether **33** permitted smooth reduction to the aldehyde **34** which was obtained as a clean single product. Reaction with the ylide formed from (4-carboxybutyl)phosphonium bromide and $NaN(TMS)_2$ in THF at −30 °C produced, after treatment with diazomethane, cis-olefin **35**[20c] in better than 95% yield. The cis stereochemistry was established by double irradiation experiments which showed a coupling constant for the olefinic protons of 10.1 Hz. The ^{19}F NMR spectrum indicated the presence of 3% of the trans isomer. It is noteworthy that using $LiN(TMS)_2$ in place of the sodium derivative gave a difficulty separable mixture of C-5 cis and trans isomers. Desilylation of **35** to **36** and triflation followed by reaction with NaN_3 in DMF produced the azide **37** which was reduced to amine **38** with PPh_3/THF/H_2O.[21] Acylation of **38** with heptanoylglycyl imidazole yielded **39** in excellent yield. Hydrolysis of the methyl ester with 0.3 N NaOH produced the target compound **6** in good yield.

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Biological Test Results and Conclusions

The DFTXA$_2$ analog **6** was tested in coronary artery preparations as a receptor antagonist versus the TXA$_2$/PGH$_2$ agonist U-46,619 (**4**) and compared with the well-characterized receptor antagonist (−)-**5**.[13] Compound **6** was found to be an antagonist with a ligand–receptor dissociation constant $K_B = 305 \pm 44$ nM. Under the same conditions (−)-**5** had $K_B = 69 \pm 13$ nM. Like (−)-**5**, **6** had no significant agonist activity at concentrations up to 10 μM.

These data show that it is possible to convert the powerful TXA$_2$/PGH$_2$ agonist DFTXA$_2$ **2**, which possesses the intact TXA$_2$ nucleus into a receptor antagonist devoid of agonist activity. It is significant that the structural modifications made for this purpose are those previously employed in the design and synthesis of the TXA$_2$/PGH$_2$ receptor antagonist (−)-**5**, whose structure resembles that of PGH$_2$. We conclude that both **6** and (−)-**5** bind to the same receptor, lending further support to the evidence for a common TXA$_2$/PGH$_2$ receptor.

Experimental Section[14]

(2*R*,3*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-(1-heptenyl)-3-(mesyloxy)-4-(benzyloxy)butane (9). To a solution of monosilyl ether (−)-**8** (16.5 g, 31.1 mmol)[14] in dry pyridine (7.5 mL, 93.4 mmol) at 0 °C was added methanesulfonyl chloride (2.9 mL, 37.3 mmol) with stirring under nitrogen for 3 h. After being stirred overnight at room temperature (19 °C) the mixture was worked up with ether and water. it was purified on silical gel with 5% EtOAc in hexane as eluant. Yield: 17.0 g (90%); $[\alpha]^{20}_D$: −2.85° (c = 1.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71–7.28 (m, 15H, 3 phenyls) 5.52 (dt, 1H, H-2′, $J_{2',1'}$ = 10.9 Hz, $J_{2',3'a}$ = 7.25 Hz, $J_{2',3'b}$ = 3.42 Hz), 5.24 (m, 2H, H-1′, and H-3), 4.54 (ABq, 2H, OCH_2Ph, J_{gem} = 16.8 Hz), 3.73 (two dd's, 2H, H-1, J_{gem} = 10.76 Hz, $J_{1a,2}$ = 7.2 Hz, $J_{1b,2}$ = 3.7 Hz), 3.58 (two dd's, 2H, H-4, J_{gem} = 9.5 Hz, $J_{3,4a}$ = 4.6 Hz, $J_{3,4b}$ = 5.1 Hz), 3.06 (s, 3H, OSO_2CH_3), 2.87 (m, 1H, H-2), 1.81 (m, 2H, H-3′), 1.25 (m, 6H, H-4′, H-5′, H-6′), 1.09 (s, 9H, $^tC_4H_9SiPh_2$), 0.87 (t, 3H, H-7′, J = 7 Hz). Anal. Calcd for $C_{35}H_{48}O_5SiS$: C, 69.04; H, 7.95. Found: C, 68.92; H, 7.83.

(2*R*,3*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-2-formyl-3-(mesyloxy)-4-(benzyloxy)butane (10). Into a solution of alkene **9** (14.65 g, 24.09 mmol) in 260 mL of dry CH_2Cl_2 containing 2 mL of MeOH (1.5 equiv) at −78 °C was bubbled a stream of ozone in oxygen until the blue color persisted. Excess of ozone was removed with N_2, and the ozonide was reduced by a 10-fold excess of dimethyl sulfide (17.65 mL). After workup with water the material was used for the next step without purification as the aldehyde was unstable on silica gel. Yield: 15.4 g (quantitative). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.83 (s, 1H, CHO), 7.7–7.2 (m, 15H, 3 phenyls), 4.74 (t, 1H, H-4, J = 5.85 Hz), 4.55 and 4.45 (ABq, 2H, OCH_2Ph, J_{gem} = 11.83 Hz), 4.07 and 4.02 (two ABq, 2H, H-2, J_{gem} = 11.1 Hz, $J_{1a,2}$ = 4.7 Hz, $J_{1b,2}$ = 4.9 Hz), 3.84 (dd, 1H, H-4a, J_{gem} = 11.43 Hz, $J_{4a,3}$ = 2.63 Hz), 3.71 (dd, 1H, H-4b, J_{gem} = 11.43 Hz, $J_{3,4b}$ = 5.95 Hz), 3.04 (s, 3H, OSO_2CH_3), 2.95 (m, 1H, H-2), 1.05 (s, 9H, $^tC_4H_9SiPh_2$).

Ethyl (3*S*,4*R*,5*S*)-2,2-Difluoro-3-hydroxy-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5-(mesyloxy)-6-(benzyloxy)hexanoate (11a,3β) and Ethyl (3*R*,4*R*,5*S*)-2,2-Difluoro-3-hydroxy-4-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5-(mesyloxy)-6-(benzyloxy)hexanoate (11b,3α). A suspension of zinc dust (5.51 g, 84.3 mmol) in 3 mL of dry THF containing 100 μL of 1,2-dibromoethane was heated to 65 °C for 1 min and then cooled to 19 °C, after which 100 μL of chlorotrimethylsilane was added. An additional 150 mL of dry THF was added and the mixture stirred for 15 min at 19 °C. A solution of the aldehyde (**10**, 13.0 g, 24 mmol) and ethyl bromodifluoroacetate (10.81 mL, 84.3 mmol) in 150 mL of THF was then added dropwise over a period of 15 min. The reaction was kept under control by immersing it into an ice bath when required. After being stirred for 30 min by which time all the zinc had dissolved, the reaction mixture was worked up as usual. The crude product was purified on a silica gel (6.5 × 30 cm) column and eluted with increasing proportions of CH_2Cl_2 in hexane. Ethyl 2,2-difluoro-3-hydroxyoctanoate (Reformatsky product from residual hexanal) was eluted first, followed by the 3β-isomer and finally the α-isomer. Total yield: 15.15 g (94.7%); ratio of β:α = 1:1.

3β-Isomer (11a). $[\alpha]^{20}_D$: −18.15° (c = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61–7.13 (m, 15H, 3 phenyls), 5.12 (m, 1H, H-5), 4.48 (dm, 1H, H-3, $J_{H,F}$ = 23.6 Hz), 4.35 (m, 3H, OCH_2Ph and OH), 4.28 (dd, 1H, H-7a, J_{gem} = 11.6 Hz, $J_{7a,4}$ = 3.8 Hz), 3.79 (brd, 1H, H-7b, J_{gem} = 11.6 Hz), 4.22 (distorted t, 2H, $CO_2CH_2CH_3$), 3.7 (dd, 1H, H-8a, J_{gem} = 11.8 Hz, $J_{8a,5}$ = 4.9 Hz) and 3.28 (dd, 1H, H-8b, J_{gem} = 11.8 Hz, $J_{8b,5}$ = 2.1 Hz), 3.05 (s, 3H, OSO_2CH_3), 2.42 (m, 1H, H-4), 1.33 (t, 3H, $CO_2CH_2CH_3$, J = 7.1 Hz), 1.06 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 112.49 (dd, $J_{F,F}$ = 259.4 Hz, $J_{H,F}$ = 10.4 Hz), 122.37 (dd, $J_{F,F}$ = 260.2 Hz, $J_{H1,F}$ = 24.9 Hz). Anal. Calcd for $C_{33}H_{42}O_8F_2SiS$: C, 59.64; H, 6.32. Found: C, 59.34; H, 6.50.

3α-Isomer (11b). $[\alpha]^{20}_D$: +5.44° (c = 1.48, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.63–7.23 (m, 15H, 3 phenyls), 5.28 (m, 1H, H-5), 4.49 (m, 3H, OCH_2Ph, H-3), 4.35 (q, 2H, $CO_2CH_2CH_3$, J = 7.1 Hz), 3.95 (dd, 1H, H-7a, J_{gem} = 10.2 Hz, $J_{7a,4}$ = 6.9 Hz), 3.88 (dd, 1H, H-7b, J_{gem} = 10.2 Hz, $J_{7b,4}$ = 5.6 Hz), 3.81 (dd, 1H, H-8a, J_{gem} = 10.9 Hz, $J_{8a,5}$ = 4.4 Hz), 3.72 (dd, 1H, H-8b, J_{gem} = 10.9 Hz, $J_{8b,5}$ = 6.8 Hz), 2.98 (s, 3H, OSO_2CH_3), 2.55 (m, 1H, H-4), 1.36 (t, 3H, $CO_2CH_2CH_3$, J = 7.1 Hz), 1.08 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 110.97 (dd, $J_{F,F}$ = 258.2 Hz, $J_{H,F}$ = 5.3 Hz), 120.48 (dd, $J_{F,F}$ = 258.1 Hz, $J_{H1,F}$ = 21.9 Hz). Anal. Calcd for $C_{33}H_{48}O_8F_2SiS$: C, 59.64; H, 6.32. Found: C, 59.49; H, 6.17.

(3*R*,4*R*,5*R*)-1-Oxo-2,2-difluoro-3α-hydroxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)methyl]-1,5-oxidopentane (14). To a solution of the 3α-hydroxy mesylate **11b** (2.32 g, 3.5 mmol) in dry DME (40 mL) was added anhydrous cesium acetate (1 g, 5.2 mmol), and the mixture was refluxed for 17 h under N_2. The product was isolated by removing DME under vacuum followed by workup with dilute HCl and ether to give a residue (partially lactonized), which lactonized completely on standing overnight at room temperature. Yield: 1.87 g (quantitative). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61–7.17 (m, 15H, 3 phenyls), 4.88 (d, 1H, H-5, $J_{4,5}$ = 7.13 Hz), 4.77 (brd, 1H, OH, J = 10.4 Hz), 4.49 (ABq, 2H, OCH_2Ph, J_{gem} = 11.7 Hz), 4.13 (m, 1H, H-3), 3.87 (dd, 1H, H-7a, J_{gem} = 10.69 Hz), 3.72 (t, 1H, H-7b, J_{gem} = 10.69 Hz, $J_{7b,4}$ = 7.15 Hz), 3.68 (dd, 1H, H-8a, J_{gem} = 11.25 Hz, $J_{8a,5}$ = 3.35 Hz), 3.53 (dd, 1H, H-8b, J_{gem} = 11.25 Hz, $J_{8b,5}$ = 2.07 Hz), 3.02 (m, 1H, H-4), 1.07 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 102.9 (dd, $J_{F,F}$ = 290.4 Hz, $J_{H3,F}$ = 6.0 Hz), 121.5 (d, $J_{F,F}$ = 283 Hz). The 3β-lactone **15** was prepared as described above. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61–7.16 (m, 15H, 3 phenyls), 4.78 (m, 1H, H-5), 4.58 (m, 1H, H-3), 4.4 (ABq, 2H, OCH_2Ph, J_{gem} = 11.65 Hz), 4.03 (dd, 1H, H-7a, J_{gem} = 10.91 Hz, $J_{7a,4}$ = 4.8 Hz), (dd, 1H, H-7b, J_{gem} = 10.91 Hz, $J_{7b,4}$ = 1.0 Hz), 3.73 (t, 1H, H-8a, J_{gem} = 10.85 Hz), 3.63 (dd, 1H, H-8b, J_{gem} = 10.85 Hz, $J_{8b,5}$ = 3.32 Hz), 2.62 (m, 1H, H-4), 1.07 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 114.88 (dd, $J_{F,F}$ = 281.8 Hz, $J_{H,F}$ = 15.2 Hz), 118.14 (dd, $J_{F,F}$ = 278 Hz, $J_{H,F}$ = 10.4 Hz).

Ethyl (3*S*,4*R*,5*S*)-2,2-Difluoro-3β-(mesyloxy)-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5β-(mesyloxy)-6-(benzyloxy)hexanoate (16). To a solution of 3β-hydroxy mesylate **11a** (1 g, 1.51 mmol) in dry pyridine (616 μL, 7.53 mmol) was added under nitrogen methanesulfonyl chloride (140 μL, 1.81 mmol) and the mixture stirred for 12 h at rt. The reaction was then diluted with ether (50 mL) and passed through a Celite pad. It was purified on silica gel with 20% EtOAc/hexane as eluant. The material crystallized on standing. Yield: 1.12 g (quantitative). Mp: 83–84 °C. $[\alpha]^{20}_D$: −5.21° (c = 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68–7.18 (m, 15 H, 3 phenyls), 5.55 (brt, 1H, H-3), 5.48 (m, 1H, H-5), 4.55 (s, 2H, OCH_2Ph), 4.2 (m, 2H, $CO_2CH_2CH_3$), 3.94 (dd, 1H, H-7a, J_{gem} = 10.6 Hz, $J_{7a,4}$ = 4.1 Hz), 3.83 (m, 3H, H-7b, H-8), 3.06 (s, 3H, C5-OSO_2CH_3), 3.03 (s, 3H, C3-OSO_2CH_3), 2.59 (m, 1H, H-4), 1.36 (t, 3H, $CO_2CH_2CH_3$), 1.09 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 113.51 and 113.25 (dd, $J_{F,F}$ = 261.5, $J_{H3,F}$ = 11.9 Hz), 114.80 and 115.07 (dd, $J_{F,F}$ = 261.5, $J_{H1,F}$ = 13.4 Hz). Anal. Calcd for $C_{34}H_{44}O_{10}F_2SiS_2$: C, 54.97; H, 5.97. Found: C, 54.72; H, 5.94.

(3*R*,4*R*,5*R*)-1-Oxo-2,2-difluoro-3α-acetoxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)methyl-1,5-oxidopentane (17). To a solution of the β-dimesylate **16** (1.1 g, 1.48 mmol) in DME (20 mL) was added cesium acetate (0.5 g, 2.6 mmol) and the reaction mixture refluxed for 22 h under N_2. The product was isolated by removing DME under vacuum, acidification with dil.HCl and extraction with ether. The crude product was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68–7.18 (m, 15 H, 3 phenyls), 5.45 (m, 1H, H-5), 4.5 (m, 2H, OCH_2Ph), 4.35 (dm, 1H, H-3, $J_{3,4}$ = 4.8 Hz, $J_{3,Fa}$ = 4.99 Hz, $J_{3,Fb}$ = 19.86 Hz), 3.75 (m, 2H, H-7), 3.6 (m, 2H, H-8), 2.45 (m, 1H, H-4, $J_{4,5}$ = 3.4 Hz), 1.01 (s, 9H, $^tC_4H_9SiPh_2$).

(3*R*,4*R*,5*R*)-1-Oxo-2,2-difluoro-3α-hydroxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)methyl]-1,5-oxidopentane (14). The α-acetoxy lactone **17** was stirred with K_2CO_3 in dry MeOH (276 mg in 20 mL, 0.1 M) for 1 h at 20 °C. The reaction was worked up by acidifying with dilute HCl and extraction with ether. The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum to give the lactone **14**. Yield: 0.8 g (quantitative).

(3*R*,4*R*,5*R*)-1-Hydroxy-2,2-difluoro-3α-hydroxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)methyl]-1,5-oxidopentane (18). A solution of the crude α-lactone **14** (2.3 g, 4.26 mmol) in dry MeOH (60 mL) was cooled to −40 °C under N_2, and $NaBH_4$ (400 mg, 10.5 mmol) was added in two portions over a period of 5 min. After 20 min at −40 °C, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc. Purification on silica gel yielded the pure α-lactol **18** on elution with 20% EtOAc/hexane followed by a small amount of the deoxygenated product **18a** (5%). Yield of **18**: 1.5 g (66%). $[\alpha]^{20}_D$: −17.67° (*c* = 6.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65–7.17 (m, 15H, 3 phenyls), 5.21 (m, 1 H, H-1), 4.56 (d, 1H, OH, *J* = 8.17 Hz), 4.41 (m, 3H, OCH_2Ph, H-5), 4.30 (m, 1H, H-3), 4.16 (t, 1H, H-7a, J_{gem} = 10.0 Hz), 3.78 (m, 1H, H-7b, J_{gem} = 10 Hz), 3.42 (dd, 1H, H-8a, J_{gem} = 10.32 Hz, $J_{8a,5}$ = 7 Hz), 3.32 (dd, 1H, H-8b, J_{gem} = 10.32 Hz, $J_{5,8b}$ = 4.5 Hz), 3.08 (d, 1H, OH, *J* = 4.77 Hz), 2.61 (m, 1H, H-4), 1.05 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): φ 121.42 (dd, $J_{F,F}$ = 251.3 Hz, $J_{H3,F}$ = 19.5 Hz), 122.61 (dm, $J_{F,F}$ = 257.2 Hz). HRMS (CI, isobutane): calcd for $C_{30}H_{36}O_5F_2Si$ (M + 1; 39.5) 543.2378, *m/z* 543.2437. **Spectral Data for 18a.** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65–7.27 (m, 15H, 3 phenyls), 4.49 (m, 3H, H-5 and OCH_2Ph), 4.36 (d, 1H, OH, *J* = 6.97 Hz), 4.28 (m, 1H, H-3, $J_{H,F}$ = 23.98 Hz, $J_{3,4}$ = 3.46 Hz), 3.94 (m, 2H, H-1), 3.87 (dd, 2H, H-7, J_{gem} = 10.76 Hz, $J_{4,7}$ = 5.5 Hz), 3.5 (t, 1H, H-8a, J_{gem} = 9.63 Hz), 3.42 (dd, 1H, H-8b, J_{gem} = 9.63 Hz, $J_{8b,5}$ = 3.73 Hz), 2.14 (m, 1H, H-4), 1.06 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): δ 115.86 (dm, $J_{F,F}$ = 253.7 Hz), 124.2 (dt, $J_{F,F}$ = 254.2 Hz, $J_{H3,F}$ = 25.8 Hz, $J_{H1,F}$ = 8.9 Hz, $J_{H1',F}$ = 13.5 Hz).

(1*R*,3*R*,4*R*,5*R*)-4α-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)methyl]-7,7-difluoro--2,6-dioxa[3.1.1]bicycloheptane (22). To a solution of PPh_3 (163 mg, 0.62 mmol) in dry CH_2Cl_2 (12 mL) at 0 °C was added freshly distilled DEAD (98 μL, 0.62 mmol) under N_2 and the mixture stirred vigorously for 5 min, following which 3α-lactol **18** (280 mg, 0.51 mmol) in CH_2Cl_2 (6 mL) was added and the solution stirred at 0 °C for 5 min and at room temperature for 25 min. The solvent was removed and the crude product chromatographed on silica gel with 10% EtOAc/hexane as eluent. Yield: 131 mg (47%). $[\alpha]^{20}_D$: +17.87° (*c* = 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$), 300 MHz): δ 7.51–7.10 (m, 15H, 3 phenyls), 5.58 (dd, 1H, H-1, $J_{H,F}$ = 4.46 Hz, $J_{1,3}$ = 2.07 Hz), 5.18 (ddd, 1H, H-3, $J_{3,Fa}$ = 7.37 Hz, $J_{3,Fb}$ = 4.54 Hz, $J_{3,4}$ = 2.79 Hz), 4.64 (m, 1H, H-5), 4.36 (ABq, 2H, OCH_2Ph, *J* = 11.9 Hz), 4.11 (t, 1H, H-8a, J_{gem} = 9.59 Hz, $J_{8a,4}$ = 5.33 Hz), 3.87 (ddd, 1H, H-8b, J_{gem} = 9.59 Hz, $J_{8b,4}$ = 1.99 Hz), 3.38 (m, 2H, H-9), 2.54 (m, 1H, H-4), 0.98 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): φ 1.03.4 (d, $J_{F,F}$ = 189.3 Hz), 133.23 (dd, $J_{F,F}$ = 189.3 Hz, $J_{H1,F}$ = 8.1 Hz). HRMS (CI, isobutane): calcd for $C_{30}H_{34}O_4F_2Si$ (M + 1, 27.4) 524.2194, *m/z* 524.2249. Anal. Calcd for $C_{30}H_{34}O_4F_2Si$: C, 68.7; H, 6.53. Found: C, 67.95; H, 6.48.

(1*R*,3*R*,4*R*,5*R*)-1α,3α-Diacetoxy-2,2-difluoro-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)methyl]-1,5-oxidopentane (23). To a solution of α-lactol **18** (10 mg, 0.02 mmol) in CH_2Cl_2 (0.5 mL) were added pyridine (70 μL, 0.53 mmol) and Ac_2O (50 μL, 0.53 mmol), and the solution was stirred overnight at room temperature. It was purified on a pipette silica gel column and the diacetate **23** eluted with 15% EtOAc/hexane. Yield: 11 mg (95%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.61–7.28 (m, 15H, 3 phenyls), 6.16 (d, 1H, H-1, $J_{H,F}$ = 7.84 Hz), 5.35 (dt, 1H, H-3, $J_{H,F}$ = 27.2 Hz, $J_{3,4}$ = 4.64 Hz), 4.66 and 4.54 (ABq, 2H, OCH_2Ph, J_{gem} = 12.2 Hz), 4.44 (brd, 1H, H-5, $J_{5,4}$ = 7.08 Hz), 3.92 (m, 3.92 (m, 3H, H-7 H-8a), 3.74 (d, 1H, H-8b, J_{gem} = 11.1 Hz), 2.51 (m, 1H, H-4), 2.18 (s, 3H, C1-$OCOCH_3$), 1.84 (s, 3H, C3-$OCOCH_3$), 0.98 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): φ 117.56 (two dt's, $J_{F,F}$ = 253.2 Hz, $J_{3,Fa}$ = 26.7 Hz, $J_{3,Fb}$ = 9.2 Hz), 122.14 (d, $J_{F,F}$ = 250.5 Hz). Anal. Calcd for $C_{34}H_{40}O_7F_2Si$: C, 65.15; H, 6.43. Found: C, 64.42; H, 6.48.

(3*R*,4*R*,5*R*)-1Hydroxy-2,2-difluoro-3α-acetoxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)methyl]-1,5-oxidopentane (24). To a solution of the diacetate **23** (11 mg, 0.018 mmol) in MeOH/H_2O (4:1) was added $NaHCO_3$ (2.1 mg, 0.025 mmol), and the solution was stirred at rt for 2 h and worked up by extraction with ether. The combined extracts were dried and evaporated to give the crude monoacetate **24**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.6–7.27 (m 15H, 3 phenyls), 5.38 (dt, 1H, H-3, $J_{3,Fa}$ = 28.3 Hz, $J_{3,Fb}$ = 7.8 Hz, $J_{3,4}$ = 4.34 Hz), 5.18 (m, 1H, H-1), 4.68 and 4.56 (ABq, 2H, OCH_2Ph, J_{gem} = 12.4 Hz), 4.61 (d, 1H, H-5, $J_{5,4}$ = 8.49 Hz), 4.01-3.87 (m 2H, H-7), 3.78 (dd, 2H, H-8, J_{gem} = 11.88 Hz), 3.65 (d, 1H, OH, *J* = 3.8 Hz), 2.44 (m, 1H, H-4), 1.82 (s, 3H, $OCOCH_3$), 0.98 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): φ 118.3 and 118.95 (two dt's, $J_{F,F}$ = 247.2 Hz, $J_{H,F}$ = 5.5 Hz) 122.02 (d, $J_{F,F}$ = 248.7 Hz).

(1*R*,3*R*,4*R*,5*R*)-1α-(Mesyloxy)-2,2-difluoro-3α-acetoxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)-methyl]-1,5-oxidopentane (25). To a solution of the monoacetate **24** (9 mg, 0.016 mmol) in CH_2Cl_2 (0.5 mL) was added pyridine (20 μL) and MsCl (10 μL) and the mixture stirred overnight at 19 °C. Purification on silica gel with 25% EtOAc/hexane as eluant yielded the pure mesylate **25**. Yield: 7 mg (69%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.6–7.2 (m, 15H, 3 phenyls), 5.82 (d, 1H, H-1, $J_{H,F}$ = 7.46 Hz), 5.32 (dt, 1H, H-3, $J_{H,F}$ = 27.46 Hz), 4.55 (m, 3H, OCH_2Ph and H-5), 3.93 (m, 3H, H-8, H-7a), 3.72 (d, 1H, H-7b, J_{gem} = 11.2 Hz), 3.16 (s, 3H, OSO_2CH_3), 2.55 (m, 1H, H-4), 1.86 (s, 3H, $OCOCH_3$), 0.996 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$), 376.2 MHz): φ 116.14 and 116.82 (two dt's, $J_{F,F}$ = 256.1 Hz, $J_{H3,F}$ = 26.2 Hz), 120.64 (d, $J_{F,F}$ = 256.0 Hz, $J_{H1,F}$ = 8.7 Hz).

(1*S*,3*R*,4*R*,5*R*)-1β-Iodo-2,2-difluoro-3α-acetoxy-4α-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-5α-[(benzyloxy)methyl]-1,5-oxidopentane (26). To a solution of the mesylate **25** (7 mg, 0.01 mmol) in DMF (0.6 mL) was added NaI (15 mg, 10 equiv; dried under vacuo at 70 °C for 10 h), and the mixture was heated to 50 °C for 12 h. The product was isolated by extraction with ether and water. Purification by PTLC on silica gel and elution with 20% EtOAc/hexane yielded **26** (2 mg, 37%) as the fast moving band followed by the starting material (2 mg). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.6–7.21 (m, 15H, 3 phenyls), 6.79 (d, 1H, H-1, $J_{H,F}$ = 12.37 Hz), 5.65 (dm, 1H, H-3, $J_{H,F}$ = 26.2 Hz), 4.6 (ABq, 2H, OCH_2Ph, J_{gem} = 12.27 Hz), 4.38 (brd, 1H, H-5), 3.99–3.68 (m, 4H, H-7, H-8), 2.54 (m, 1H, H-4), 1.8 (s, 3H, $OCOCH_3$), 0.93 (s, 9H, $^tC_4H_9SiPh_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): φ 108.9 (d, $J_{F,F}$ = 235.9 Hz), 112.6 and 113.22 (two ddd's, $J_{F,F}$ = 235.6 Hz, $J_{H3,F}$ = 27.2 Hz, $J_{H1,F}$ = 14.2 Hz, $J_{H1',F}$ = 5.7 Hz).

(1*R*,3*R*,4*R*,5*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-5α-(benzyloxy)-methyl-7,7-difluoro-2,6-dioxa[3.1.1]bicycloheptane (22). To a solution of the 1β-iodo compound **26** (2 mg, 0.003 mmol) in MeOH/H_2O (0.24 mL/0.06 mL) was added 0.3 mL of 0.1 M K_2CO_3 solution [prepared by dissolving 138 mg of K_2CO_3 in MeOH (8 mL) and H_2O (2 mL)] and the mixture stirred at rt for 12 h. The product was isolated by extraction with ether and purified on silica gel with 10% EtOAc/hexane as eluant. The first fraction (1 mg) contained the pure oxetane (**22**), identical by TLC and ^{1}H and ^{19}F NMR with the product obtained in the Mitsunobu reaction. The second fraction (0.5 mg) consisted of the desilylated oxetane (**27**).

(1*R*,3*R*,4*R*,5*R*)-4α-(Hydroxymethyl)-5α-[(benzyloxy)-methyl]-7,7-difluoro-2,6-dioxa[3.1.1]bicycloheptane (27). To a solution of the oxetane **22** (441 mg, 0.84 mmol) in dry THF (15 mL) under N_2 at 0 °C was added Bu_4NF (1M solution in THF, 1.09 mL, 1.09 mmol) and the mixture stirred at 0 °C for 1 h and then quenched with saturated NH_4Cl and extracted with EtOAc.

The crude product **27** was purified by flash chromatography on silica gel with EtOAc/hexane (40%) as eluant. Yield: 213.3 mg (89%). $[\alpha]^{20}_D$: +27.9° (c = 1.75, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 5H, $OCH_2C_6H_5$), 5.58 (m, 1H, H-1), 5.0 (m, 1H, H-3), 4.71 (m, 1H, H-5), 4.6 (s, 2H, OCH_2Ph), 4.06 (dd, 1H, H-8a, J_{gem} = 11.09 Hz, $J_{8a,4}$ = 6.38 Hz), 3.92 (brt, 1H, H-8b), 3.79 (dd, 1H, H-9a, J_{gem} = 10.08 Hz, $J_{9a,5}$ = 7.2 Hz), 3.69 (dd, 1H, H-9b, J_{gem} = 10.08 Hz, $J_{5,9b}$ = 5.53 Hz), 2.6 (q, 1H, H-4, $J_{4,8}$ = 6.65 Hz), 2.55 (brs, 1H, OH). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 104.2 (d, $J_{F,F}$ = 185.9 Hz), 134.15 ($J_{F,F}$ = 185.3 Hz, $J_{H1,F}$ = 8.3 Hz). Anal. Calcd for $C_{14}H_{16}O_4F_2$: C, 58.73; H, 5.63. Found: C, 58.83; H, 5.90.

(1*R*,3*R*,4*R*,5*R*)-4α-[[(Methanesulfonyl)oxy]methyl]-5α-[(benzyloxy)methyl]-7,7-difluoro-2,6-dioxa[3.1.1]bicycloheptane (29). To a solution of the oxetanemethanol **27** (213 mg, 0.74 mmol) in dry pyridine (601 μL, 7.4 mmol) at 0 °C under N_2 was added distilled MsCl) (89 μL, 1.15 mmol) and the reaction mixture stirred at 0 °C for 1 h. Dilution with ether and filtering off the residue gave the crude mesylate **29**. It was purified by flash chromatography on silica gel with 20% EtOAc/hexane as eluant. Yield: 254 mg (94%). $[\alpha]^{20}_D$: +20.33° (c = 0.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39–7.26 (m, 5H, $OCH_2C_6H_5$), 5.61 (m, 1H, H-1), 5.0 (m, 1H, H-3), 4.72 (m, 1H, H-5), 4.65–4.56 (m, 4H, H-8a, H-8b, OCH_2Ph), 3.58 (m, 2H, H-9a, H-9b), 2.99 (s, 3H, OSO_2CH_3), 2.79 (brq, 1H, H-4).

(1*R*,3*R*,4*R*,5*R*)-4α-(Cyanomethyl)-5α-[(benzyloxy)-methyl]-7,7-difluoro-2,6-dioxa[3.1.1]bicycloheptane (30). To a suspension of NaCN (85 mg, 1.73 mmol, dried overnight under vacuum) in DMF (8 mL) under N_2 was added a solution of the mesylate **29** (250 mg, 0.69 mmol) in DMF (1 mL) and the reaction mixture washed at 30 °C for 17 h. The reaction was quenched with water and extracted with ether. It was purified by flash chromatography on silica gel with increasing concentration of EtOAc in hexane. The elimination product (**31**; 4 mg) was eluted first, followed by the nitrile **30**, the THF derivative **28** (1 mg), and finally the starting mesylate (160 mg). Yield of **30**: 55 mg (75% based on the consumed mesylate). $[\alpha]^{20}_D$: +38.57° (c = 0.07, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39–7.27 (m, 5H, $OCH_2C_6H_5$), 5.58 (m, 1H, H-1), 5.04 (m, 1H, H-3), 4.71 (m, 1H, H-5), 4.56 (ABq, 2H, OCH_2Ph, J_{gem} = 11.85 Hz), 3.61 (dd, 1H, H-9a, J_{gem} = 10.04 Hz, $J_{9a,5}$ = 5.3 Hz), 3.49 (brt, 1H, H-9b), 2.9 (m, 2H, H-8a, H-8b), 2.72 (brq, 1H, H-4). HRMS (CI, isobutane): calcd for $C_{15}H_{15}NO_3F_2$ (M+1, 100) 296.1098, m/z 296.1130. Anal. Calcd for $C_{15}H_{15}NO_3F_2$: C, 61.01; H, 5.12. Found: C, 60.40; H, 5.18.

Data for 31. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.46–7.26 (m, 5H, $OCH_2C_6H_5$), 5.7 (d, 1H, H-1, $J_{H,F}$ = 4.03 Hz), 5.21 (m, 2H, H-8a, H-8b), 5.07 (brt, 1H, H-3), 4.93 (m, 1H, H-5), 4.62 (ABq, 2H, OCH_2Ph, J_{gem} = 12.04 Hz), 3.75 (dd, 1H, H-9a, J_{gem} = 10.2 Hz, $J_{9a,5}$ = 7.37 Hz), 3.66 (dd, 1H, H-9b, J_{gem} = 10.2 Hz, $J_{9b,5}$ = 4.94 Hz). ^{19}F NMR ($CDCl_3$, 500 MHz): ϕ 103.47 (d, $J_{F,F}$ = 183.5 Hz), 136.66 (dd, $J_{F,F}$ = 183.3 Hz, $J_{H1,F}$ = 4.9 Hz).

Data for 28. ^1H NMR ($CDCl_3$, 500 MHz): δ 5.61 (brs, 1H, H-1), 4.82 (m, 1H, H-3), 4.12 (m, 2H, H-8a, H-8b), 4.0 (brt, 1H, H-5, J = 8.7 Hz), 3.92 (m, 2H, H-9a, H-9b), 2.87 (m, 1H, H-4). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 107.57 (d, $J_{F,F}$ = 186.9 Hz), 137.66 (dd, $J_{F,F}$ = 186.5 Hz, $J_{H1,F}$ = 8.2 Hz).

(1*R*,3*R*,4*R*,5*R*)-4α-(Cyanomethyl)-5α-(hydroxymethyl)-7,7-difluoro-2,6-dioxa[3.1.1]bicycloheptane (32). To a suspension of 10% Pd on carbon (20 mg) in dry 2-propanol (1 mL) was added the benzyl ether **29** (76 mg, 0.26 mmol), and after evacuation, hydrogen was admitted. After the solution was stirred at 19 °C for 25 h, CH_2Cl_2 was added and the mixture filtered through a Celite pad. Evaporation gave the crude nitrile alcohol **32**. It was purified by flash chromatography on silica gel with 30% EtOAc/hexane. Yield: 40 mg (94%). $[\alpha]^{20}_D$: +43.62° (c = 0.076, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 5.64 (m, 1H, H-1), 5.04 (m, 1H, H-3), 4.61 (m, 1H, H-5), 3.79 (m, 2H, H-9a, H-9b), 3.05 (dd, 1H, H-8a, J_{gem} = 16.82 Hz, $J_{8a,4}$ = 11.15 Hz), 2.92 (dd, 1H, H-8b, J_{gem} = 16.82 Hz, $J_{8b,4}$ = 5.0 Hz), 2.08 (distorted p, 1H, H-4), 1.99 (t, 1H, OH, J = 5.45 Hz). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 103.2 (d, $J_{F,F}$ = 193.2 Hz), 133.05 (dd, $J_{F,F}$ = 193.3 Hz, $J_{H1,F}$ = 8.7 Hz).

(1*R*,3*R*,4*R*,5*R*)-4α-(Cyanomethyl)-5α-[[(*tert*-butyldimethylsilyl)oxy]methyl]-7,7-difluoro-2,6-dioxa[3.1.1]bicycloheptane (33). To a solution of the cyano alcohol **32** (12 mg, 0.059 mmol) in CH_2Cl_2 (0.6 mL) was added DMAP (7.8 mg, 0.064 mmol) and NEt_3 (13 μL, 0.093 mmol) and then TBDMSCl (10.7 mg, 0.071 mmol). The reaction mixture was stirred at 19 °C under N_2 for 8 h. The solvent was removed, and the nitrile **33** was purified on silica with 1% EtOAc/hexane as eluant. Yield: 16 mg (85.5%). $[\alpha]^{20}_D$: +46.3° (c = 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 5.57 (m 1H, H-1), 5.06 (m, 1H, H-3), 4.51 (m, 1H, H-5), 3.78 (dd, 1H, H-9a, J_{gem} = 10.9 Hz, $J_{9a,5}$ = 4.69 Hz), 3.59 (t, 1H, H-9b), 3.06 (dd, 1H, H-8a, J_{gem} = 16.54 Hz, $J_{8a,4}$ = 11.7 Hz), 2.96 (dd, 1H, H-8b, J_{gem} = 16.54 Hz, $J_{8b,4}$ = 4.3 Hz), 0.93 (s, 9H, $^tC_4H_9SiMe_2$), 0.12 and 0.117 (two s's, 6H, $^tC_4H_9SiMe_2$). ^{19}F NMR ($CDCl_3$, 376.2 MHz): ϕ 102.45 (d, $J_{F,F}$ = 190.7 Hz), 132.81 (dd, $J_{F,F}$ = 190.7 Hz, $J_{H1,F}$ = 8.4 Hz).

(1*R*,3*R*,4*R*,5*R*)-4-(2-Oxoethyl)-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-7,7-difluoro-2,6-dioxa[3.1.1]bicycloheptane (34). A solution of the nitrile **33** (13 mg, 0.041 mmol) in dry CH_2Cl_2 (0.6 mL) was cooled to −40 °C, DIBALH (1 M solution in CH_2Cl_2, 49 μL, 0.049 mmol) was added, and the mixture was stirred at −40 °C for 1.5 h. The reaction was quenched with saturated NH_4Cl solution, and CH_2Cl_2 was removed with a stream of N_2. After the pH was lowered to 3.0 with dilute HCl the clear solution was stirred for 5 min and extracted with CH_2Cl_2. The crude aldehyde **34** obtained by evaporation at −5 °C was used for the next step without further purification. Yield: 10 mg (76%). ^1H NMR ($CDCl_3$, 500 MHz): δ 9.79 (s, 1H, CHO), 5.32 (m, 1H, H-1), 4.83 (t, 1H, H-3, $J_{3,4}$ = 5.7 Hz), 4.51 (m, 1H, H-5), 3.75 (dd, 1H, H-9a, J_{gem} = 10.8 Hz, $J_{9a,5}$ = 4.9 Hz), 3.66 (brt, 2H, H-9b), 3.18–3.0 (m, 3H, H-8a, H-8b, H-4), 0.91 (s, 9H, $^tC_4H_9SiMe_2$), 0.12 and 0.10 (s's, 6H, $^tC_4H_9SiMe_2$).

Methyl (1*R*,3*R*,4*R*,5*R*)-7′-[5-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-7,7-difluoro-2,6-dioxa[3.1.1]bicyclohept-4-yl]-5′-heptenoate (35). To a stirred solution of (4-carboxybutyl)-triphenylphosphonium bromide (36 mg, 0.08 mmol) in THF (0.5 mL) at 0 °C was added $NaN(TMS)_2$ (1 M solution in THF, 162 μL, 0.16 mmol). The resulting orange solution was stirred at 0 °C for 0.5 h and then cooled to −30 °C. The aldehyde **34** (10 mg, 0.031 mmol) dissolved in THF (300 μL) was added, and the resulting mixture was stirred for 2 h at −30 °C and then at 0 °C for 8 h. It was quenched with saturated NH_4Cl solution, the solvent removed under N_2, and the pH brought to 3.0 with dilute HCl. Extraction with EtOAc yielded the crude acid which was esterified with ethereal CH_2N_2 in methanol. Removal of the solvent and purification by pipette column chromatography on silica gel yielded the 5′-cis methyl ester **35**. The product could not be freed from impurities and was used for the next step without further purification. Yield: 8.3 mg (64%).

Methyl (1*R*,3*R*,4*R*,5*R*)-7′-[5-(Hydroxymethyl)-7,7-difluoro-2,6-dioxa[3.1.1]bicyclohept-4-yl]-5′-heptenoate (36). To a solution of the silyl ether **35** (13 mg, 0.031 mmol) in dry THF (1 mL) at 0 °C under N_2 was added Bu_4NF (1 M solution in THF, 46 μL, 0.046 mmol) and the reaction mixture stirred for 1 h at 0 °C. It was quenched with saturated NH_4Cl solution and extracted with ether. The crude alcohol **36** was purified on silica with 25% EtOAc/hexane as eluant. Yield: 8 mg (85%). $[\alpha]^{20}_D$: −4.81° (c = 0.04, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.61 (m, 1H, H-1), 5.52 (m, 1H, H-5′), 5.28 (m, 1H, H-6′), 4.76 (m, 1H, H-3), 4.57 (m, 1H, H-5), 3.77 (m, 2H, H-8′a, H8′b), 3.68 (s, 3H, CO_2CH_3), 2.67 (m, 1H, H-4), 2.35 (m, 1H, -H-7′a), 2.34 (t, 2H, H-2′a, H-2′b, J = 7.44 Hz), 2.27 (m, 1H, H-7′b), 2.09 (m, 2H, H-4′a, H-4′b, OH), 1.72 (p, 2H, H-3′a, H-3′b, J = 7.44 Hz). ^{19}F MNR ($CDCl_3$, 376.2 MHz): ϕ 104.62 (d, $J_{F,F}$ = 188.8 Hz), 133.78 (dd, $J_{F,F}$ = 189.3 Hz, $J_{H1,F}$ = 9.6 Hz). HRMS (CI, isobutane): Calcd for $C_{14}H_{20}F_2O_5$ (M + 1, 0.6) 307.1357, m/z 307.1386.

Methyl (1*R*,3*R*,4*R*,5*R*)-7′-[5-(Azidomethyl)-7,7-difluoro-2,6-dioxa[3.1.1]bicyclohept-4-yl]-5′-heptenoate (37). To a solution of the alcohol **36** (8 mg, 0.026 mmol) in dry CH_2Cl_2 (1 mL) at −22 °C under N_2 was added pyridine (21 μL, 0.26 mmol) and then freshly distilled triflic anhydride (6.6 μL, 0.039 mmol) and the reaction mixture stirred at −22 °C for 5 min. It was diluted with ether, filtered through a Celite pad, concentrated, and used for the next step immediately. The triflate (in 100 μL of DMF) was added to a suspension of NaN_3 (20 mg, 0.31 mmol) in DMF (0.6 mL) and the mixture stirred overnight at 19 °C. The product was isolated by quenching with water and extracting with ether. The crude azide **37** was purified on silic gel with 20% EtOAc/hexane as eluant. Yield: 4.6 mg (54%). ^1H NMR ($CDCl_3$,

500 MHz): δ 5.61 (m, 1H, H-1), 5.57 (m, 1H, H-5′), 5.29 (m, 1 H, H-6′), 4.77 (m, 1H, H-3), 4.64 (m, 1H, H-5), 3.69 (s, 3H, CO_2CH_3), 3.56 (dd, 1H, H-8a, J_{gem} = 12.25 Hz, $J_{8a,5}$ = 4.74 Hz), 3.35 (dd, 1H, H-8′b, J_{gem} = 12.25 Hz, $J_{8'b,5}$ = 7.28 Hz), 2.65 (m, 1H, H-4), 2.4–2.14 (m 6H, H-1′, H-7′, H-4′) 1.73 (p, 2H, H-3′, J = 7.4 Hz). 1.73 (p, 2H, H-3′, J = 7.4 Hz). ^{19}F NMR ($CDCl_3$, 376.2 MHz): φ 103.6 (d, $J_{F,F}$ = 189.0 Hz), 133.45 (dd, $J_{F,F}$ = 189.3 Hz, $J_{H1,F}$ = 7.9 Hz). FTIR (neat): 2105 (N_3) and 1732 cm^{-1} (CO_2Me).

Methyl (1*R*,3*R*,4*R*,5*R*)-7′-[5-(Aminomethyl)-7,7-difluoro-2,6-dioxa[3.1.1]bicyclohept-4-yl]-5′-heptenoate (38). To a solution of the azide **37** (2 mg, 0.006 mmol) in THF/H_2O (500 μL/2 μL) was added PPh_3 (3 mg, 0.011 mmol) and the solution stirred for 18 h at 19 °C. The solvent was removed, and the amine **38** was purified on a pipette silica gel column with 10% MeOH in CH_2Cl_2 as eluant. Yield: 1 mg (56%). ^1H NMR ($CDCl_3$, 500 MHz): δ 5.59 (m, 1H, H-1), 5.52 (m, 1H, H-5′), 5.27 (m, 1H, H-6′), 4.75 (m, 1H, H-3), 4.49 (m, 1H, H-5), 3.68 (s, 3H, CO_2CH_3), 3.03–2.88 (m, 2H, H-8′), 2.61 (m, 1H, H-4), 2.37–2.09 (m, 6H, H-7′, H-4′, H-2′), 1.73 (p, 2H, H-3′, J = 7.4 Hz). ^{19}F NMR ($CDCl_3$, 376.2 MHz): φ 103.36 (d, $J_{F,F}$ = 186.5 Hz), 133.01 (dd, $J_{F,F}$ = 189.3 Hz, $J_{H1,F}$ = 8.0 Hz).

Methyl(1*R*,3*R*,4*R*,5*R*)-7′-[5-[[[(*n*-Heptanoylamino)acetyl]-amino]methyl]-7,7-difluoro-2,6-dioxa[3.1.1]bicyclohept-4-yl]-5′-heptenoate (39). To a solution of *N*-heptanoylglycine (1.87 mg, 0.01 mmol) in dry THF (0.2 mL) was added 1,1′-carbonyldiimidazole (1.62 mg, 0.01 mmol) with stirring at 19 °C for 2 h. The amine **38** (1 mg, 0.0033 mmol) was added in THF (100 μL) and the solution stirred overnight. The solvent was removed under N_2 and the residue purified on silica gel with 35% EtOAc/hexane as eluant which yielded the pure amido amide **39**. Yield: 1.3 mg (84%). $[\alpha]^{20}_D$: −12.08° (c = 0.012, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ 6.41 (m, 1H, NH-9), 6.39 (m, 1H, NH-12), 5.54 (m, 2H, H-1, H-5′), 5.27 (m, 1H, H-6′), 4.76 (m, 1H, H-3), 4.54 (m, 1H, H-5), 3.94 (m, 2H, H-11), 3.82 (m, 1H, H-8a), 3.69 (s, 3H, CO_2CH_3), 3.27 (m, 1H, H-8b), 2.61 (m, 2H, H-4′), 2.4 (m, 1H, H-7a), 2.34 (t, 2H, H-14, J = 7.3 Hz), 2.26 (t, 2H, H-2′, J = 7.6 Hz), 2.22 (m, 1H, H-7′b), 2.11 (m, 2H, H-4′), 1.67 (m, 4H, H-3′, H-15), 1.31 (m, 6H, H-16, H-17, H-18), 0.91 (t, 3H, H-19, J = 6.38 Hz). ^{19}F NMR ($CDCl_3$), 376.2 MHz): φ 104.15 (d, $J_{F,F}$ = 189.3 Hz), 133.73 (dd, $J_{F,F}$ = 189.5 Hz, $J_{H1,F}$ = 5.3 Hz).

(1*R*,3*R*,4*R*,5*R*)-7′-[5-[[[(*n*-Heptanoylamino)acetyl]amino]-methyl]-7,7-difluoro-2,6-dioxa[3.1.1]bicyclohept-4-yl]-5′-heptenoic Acid (6). A solution of the methyl ester **39** approximately 1 mg in MeOH/H_2O (250 μL/100 μL) was treated with NaOH (1 N, 150 μL) and then stirred for 1 h at 20 °C. The acid **6** was isolated by lowering the pH to 4.0 with 0.1 N HCl extraction with EtOAc. Its precise weight was determined by the NMR integration method using methyl *tert*-butyl ether as the standard. Yield: 276 μg. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.77 (m, 1H, NH-9), 6.41 (m, 1H, NH-10), 5.58 (m, 2H, H-1, H-5′), 5.34 (m, 1H, H-6′), 4.8 (m, 1H, H-3), 4.59 (m, 1H, H-5), 4.20 (dd, 1H, H-11a, J_{gem} = 16.12 Hz, $J_{11a,12}$ = 5.9 Hz), 3.98 (dd, 1H, H-11b, J_{gem} = 16.12 Hz), 3.67 (brs, 1H, CO_2H), 3.62 and 3.53 (m, 2H, H-8), 2.57 (m, 1H, H-4), 2.46 (m, 1H, H-7′a), 2.38 (t, 2H, H-14, J = 6.2 Hz), 2.33 (m, 1H, H-7′b), 2.27 (t, 2H, H-2′, J = 7.6 Hz), 2.20 and 2.09 (m, 2H, H-4′), 1.81–1.61 (m, 4H, H-3′, H-15), 1.48–1.23 (m, 6H, H-16, H-17, H-18), 0.91 (t, 3H, H-19, J = 6.4 Hz). ^{19}F NMR ($CDCl_3$, 376.2 MHz): φ 104.51 (d, $J_{F,F}$ = 189.0 Hz), 133.95 (dd, $J_{F,F}$ = 190.0 Hz, $J_{F,F}$ = 8.1 Hz).

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Supplementary Material Available: Proton (500-MHz) NMR spectra of compounds **10, 14, 15, 18a, 23–26, 28, 29, 31–34, 36–39,** and **6** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.