Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 15 (2007) 5509–5518
Bioorganic & Medicinal Chemistry

Antiproliferative, low-calcemic, fluorinated sulfone analogs of 1α,25-dihydroxyvitamin D_3: Chemical synthesis and biological evaluation

Aimee R. Usera,[a] Patrick M. Dolan,[b] Thomas W. Kensler[b] and Gary H. Posner[a,*]

[a]*Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, MD 21218, USA*
[b]*Division of Toxicology, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, MD 21205, USA*

Received 13 April 2007; revised 16 May 2007; accepted 18 May 2007
Available online 25 May 2007

Abstract—Novel fluorinated sulfone analogs of the hormone 1α,25-dihydroxyvitamin D_3 have been designed and synthesized in order to study the biological effects of fluorine incorporation at the terminus of the C,D-ring side chain. Although biologically active 26,27-hexafluorinated 1α,25-dihydroxyvitamin D_3 analogs have been synthesized previously, this investigation reports the first successful fluorinated series in which trifluoromethyl sulfone analogs present a favorable biological profile. This study shows that two new analogs featuring incorporation of a synthetically simple single trifluoromethyl sulfone group have significantly increased antiproliferative activity while causing desirably low in vivo calciuria relative to that of calcitriol. Incorporation of additional fluorines, as in a perfluorobutyl analog, results in a loss of antiproliferative activity.

1. Introduction

The hormone 1α,25-dihydroxyvitamin D_3, more commonly known as calcitriol (**1**) (Fig. 1), has been recognized to be essential to human health for many decades. First discovered as a treatment for the disease rickets in late 18th century,[1] this compound retains its value in the present day by participating in cell differentiation, immunology, regulation of gene transcription, and a number of other biological activities.[2] These more recently discovered biological activities allow for application of vitamin D_3 to the treatments of diseases such as psoriasis, leukemia, breast and skin cancers, and prostate cancer.[1] Although calcitriol's biological importance is well established, a continuing challenge in vitamin D research is to achieve an optimal balance between high antiproliferative activity and low calcemic activity. There are several ways to approach this issue: increasing the bioavailability of the compound, blocking the catabolic pathway[3] to avoid degradation, and increasing the interactions between the vitamin D receptor (VDR)[3a,4] and the hormone, 1α,25-dihydroxyvitamin D_3 (**1**). One modification of 1α,25-dihydroxyvitamin D_3 (**1**) that considers all of these approaches is the incorporation of one or more fluorine atoms.

Fluorinated compounds comprise some of the most successful pharmaceuticals on the market today including the antidepressants Prozac® (Eli Lilly) and Paxil®, and the widely prescribed antibiotic Ciproflaxin® (Bayer). The incorporation of fluorine is a simple method of modification which oftentimes results in a better medicinal candidate compared to the lead compound.[5,6] Research has shown that, in general, fluorinated compounds require a far lower effective dosage than their analogous non-fluorinated pharmaceuticals.[5] The introduction of a fluorine atom into Cipro actually increased the rate of cell penetration by up to 70 times.[7]

The fluorine atom is strongly electronegative,[5,6,8] possibly leading to increased interactions between calcitriol and the VDR. The atom is sterically comparable to hydrogen[6–8] which creates no increased steric hindrance for VDR binding. In addition, fluorine forms the strongest covalent bond[6,8] with carbon which may hinder the catabolic pathway. These favorable characteristics, in addition to the synthetic simplicity of fluorine incorporation, make fluorine an excellent and simple candidate for approaching vitamin D_3 analog design and synthesis.

Keywords: Vitamin D_3; Fluorinated sulfones; Trifluoromethyl; Calcitriol.
* Corresponding author. E-mail: ghp@jhu.edu

0968-0896/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2007.05.051

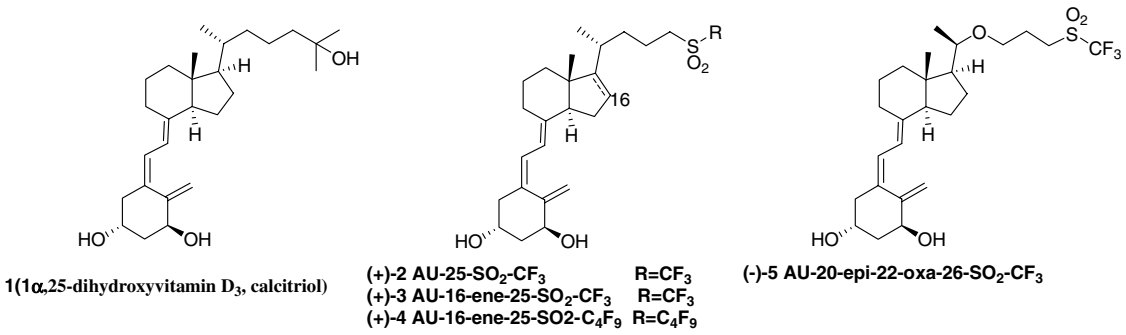


Figure 1. 1α, 25-dihydroxyvitamin D_3 and newly developed fluorosulfone analogs.

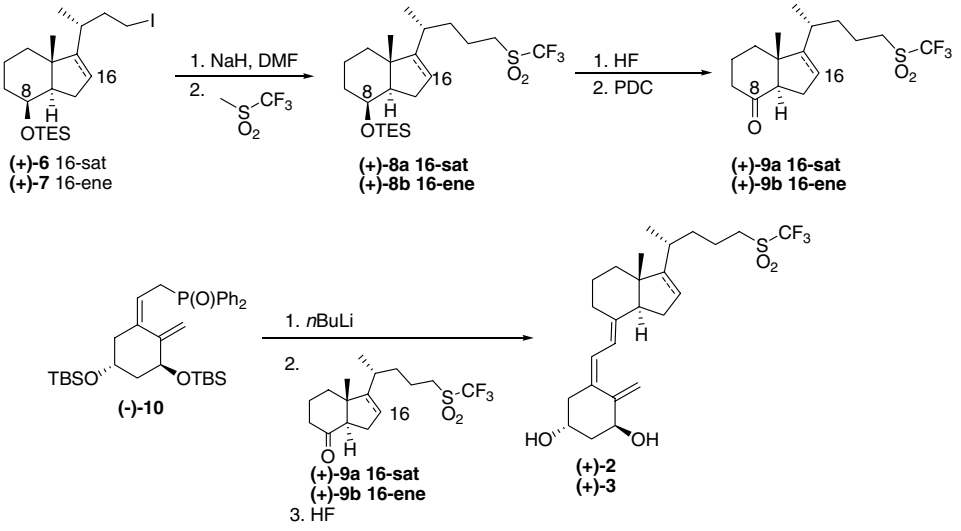
There are several instances of incorporation of fluorine into the vitamin D_3 structure[9] to create a biologically active analog. One such case is Hoffmann LaRoche's extremely successful Ro24-5531 containing a 26,27-hexafluorinated side chain.[10] Although there are many examples of fluorinated compounds, no vitamin D_3 analogs to date have incorporated a single trifluoromethyl sulfone group into the terminus of the C,D-ring side chain. We have previously synthesized 25- and 26-*tert*-butyl sulfone analogs having antiproliferative activity comparable to that of calcitriol and calcemic levels significantly lower than that of the natural hormone.[11,12] In attempts to improve the antiproliferative activity of these *tert*-butyl sulfone analogs, we prepared a series of fluorinated compounds.

2. Results and discussion

2.1. Chemistry

Synthesis of analogs **(+)-AU-25-SO$_2$-CF$_3$ (2)** and **(+)-AU-16-ene-25-SO$_2$-CF$_3$ (3)**, outlined in Scheme 1, begins with previously reported 23-iodides **(+)-6**[13] and **(+)-7**.[11] Simple displacement of the iodide with the corresponding conjugate base of the methyl fluorinated sulfone,[14] followed by C-8 deprotection and subsequent oxidation, furnished the desired C-8 ketones **(+)-9**. Each C-8 ketone was then reacted with enantiomerically pure A-ring[13] **(−)-10** in a Horner–Wadsworth–Emmons coupling followed by deprotection of the C-1 and C-3 alcohols to obtain the desired analogs **(+)-2** and **(+)-3**.

The synthesis of the 20-epi-22-oxa 26-SO$_2$-CF$_3$ side chain was more complicated as illustrated in Scheme 2. Ketone **(+)-11** was prepared as previously reported.[12] Due to competition of the C-8 silyl protecting group during reductive etherification, the C-8-OTES group was deprotected and then converted into the acetate. The trifluoromethyl sulfonyl side chain **13** was installed through a reductive etherification[12] with C-20 ketone **(+)-12** to give 20-epi-22-oxa-27-SO$_2$-CF$_3$ **(−)-14**. The 20-epi configuration was confirmed by a ^{1}H NMR upfield shift of the 21-methyl group from approximately 0.68 to 0.54 ppm. The characteristic shift to 0.54 ppm correlates with previously synthesized 20-epi analog, KRC-20-epi-22-oxa-26-SO2-1.[12] With verification of the formation of the desired 20-epi stereocenter, C-8 acetate was deprotected followed by oxidation to give C-8 ketone **(−)-15**. Deprotection of the acetate in the presence of the trifluoromethyl group proved problematic. However, by the use of diisobutylaluminum



Scheme 1.

hydride (DIBAL-H) at −78 °C the reduction of the acetate was achieved. Ketone **(−)-15** was then coupled with the enantiomerically pure A-ring **(−)-10**, and subsequent deprotection yielded the desired analog **(−)-AU-20-epi-22-oxa-26-SO_2-CF_3 (5)**.

2.2. Biology

The in vitro antiproliferative activities of fluorinated sulfones **2**–**5** and calcitriol, determined using our standard murine keratinocyte assay,[15] are displayed in Figure 2. Trifluoromethyl sulfone analog **2**, saturated at the 16 position, has antiproliferative activity no greater than that of the parent hormone, calcitriol (**1**) (Fig. 2). In attempts to increase this activity, we designed the 16-ene form of this analog. Although more synthetically challenging, unsaturation at the 16 position is known to increase the antiproliferative activity of a compound.[3a,16] This alteration did, in fact, lead to the highly active fluorinated sulfone **3** which has greater antiproliferative activity than calcitriol (**1**) even at a concentration of 7 nM (Fig. 2). With this exciting result, we designed nona-fluorobutylsulfone **4**, which would possibly increase the lipophilicity due to an increase in the number of fluorines. In addition, promising results with 26,27-hexafluorinated vitamin D_3 analogs[9,10] indicate that more than three fluorine atoms may create a more biologically active compound. However, the C_4F_9 sulfone **4** is only slightly antiproliferative at a high concentration of 1.0 μM, not even comparable to calcitriol (**1**) (data not shown). The low antiproliferative activity of this nona-fluoro-compound might result from too many fluorine atoms making the molecule too lipophilic and

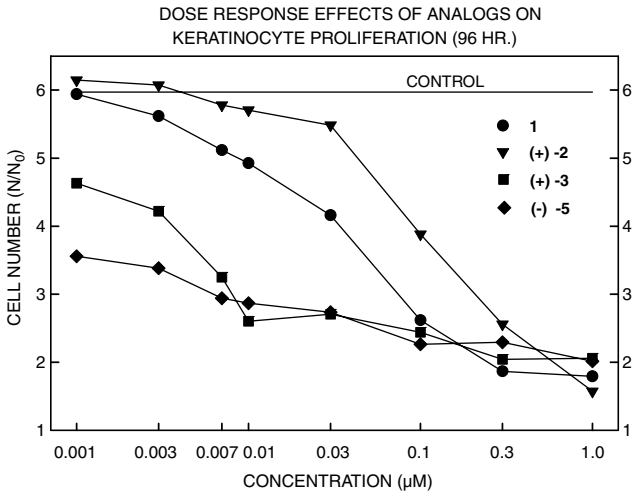
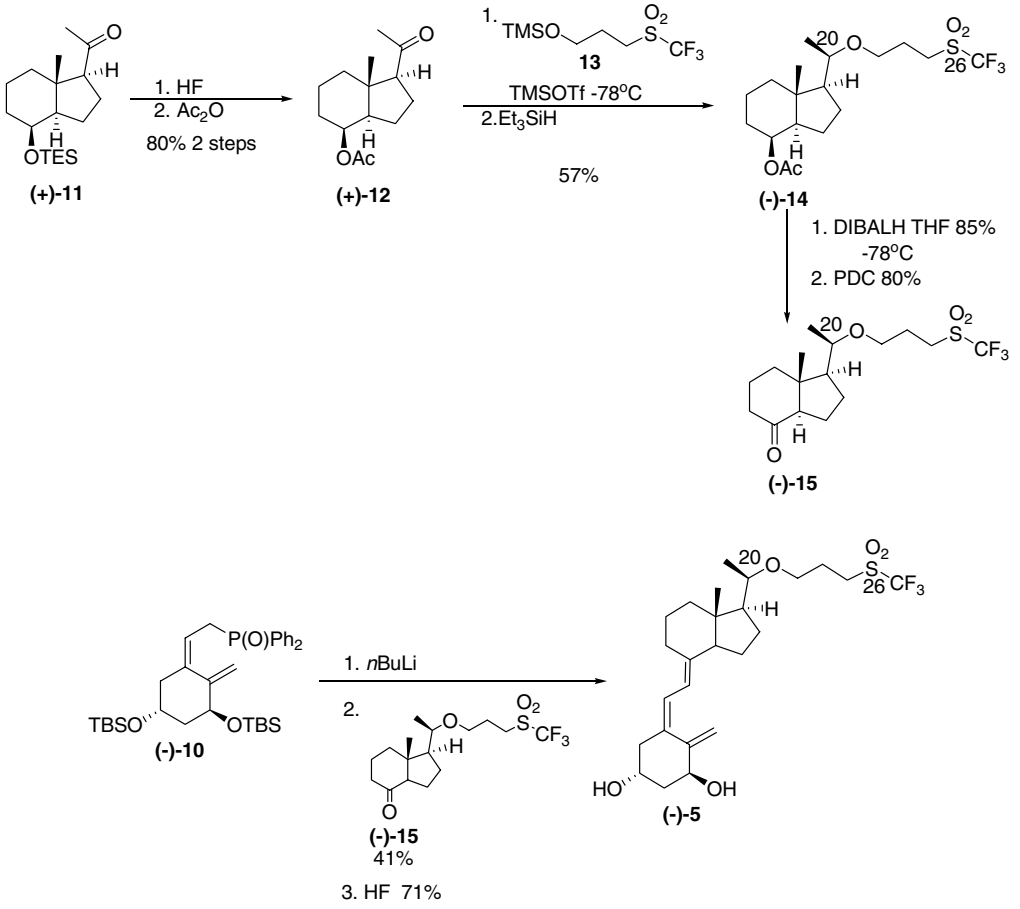


Figure 2. Antiproliferative effects of trifluoromethyl sulfone analogs of vitamin D_3.



Scheme 2.

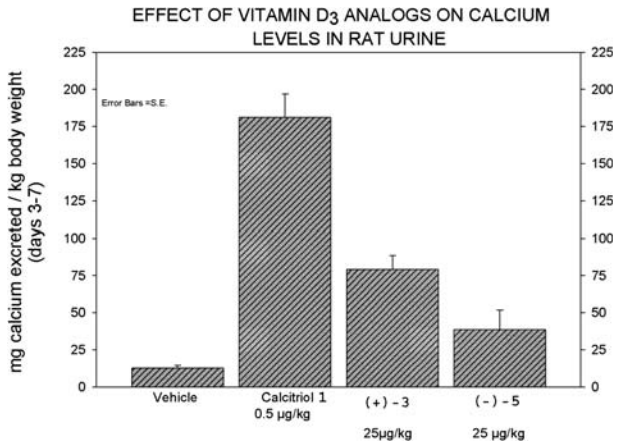


Figure 3. Effects of vitamin D_3 analogs on urinary calcium excretion in rats.

less bioavailable. The poor antiproliferative activity may also be due to the length of the side chain which could create a steric hindrance between the vitamin D side chain and the VDR binding site making the necessary interactions difficult.

The final 20-epi-22-oxa 27-trifluorosulfone analog **5** was designed based on a previously synthesized 20-epi-22-oxa 26-*tert*-butyl sulfone which displays high antiproliferative activity.[12] Terminally fluorinated analog **5** shows excellent antiproliferative activity even at 3–7 nM concentrations (Fig. 2).

The antiproliferative profiles of fluorinated sulfones **3** and **5** are excellent. However, the calcemic levels of these molecules must also be considered for practical medicinal purposes. Using our previously reported protocol in which rats are treated orally with 1α,25-dihydroxyvitamin D_3 (**1**) or with the new analogs daily for one week,[11] the two highly antiproliferative fluorinated sulfones **3** and **5** show calciuria levels far below that of calcitriol even at fifty times the concentration of the parent hormone (Fig. 3).

3. Conclusion

In conclusion, we have shown, for the first time, that fluorination of the 26 or 27 position of 1α,25-vitamin D_3 sulfone analogs in the form of a single trifluoromethyl group produces high antiproliferative activity while diminishing calcemic activity. These analogs may have enhanced bioavailability due to increased lipophilicity. They may also participate in hydrogen bonding, of which analogous *tert*-butyl analogs are not capable. These terminally fluorinated analogs may also block cytochrome P450-mediated catabolism, prolonging the half-life of the molecule which results in a more active compound. Lastly, the steric differences must be taken into consideration. The trifluoromethyl group is smaller than the *tert*-butyl group and may make a better fit into the VDR active site. We are currently investigating these hypotheses by synthesizing and analyzing novel analogs that are sterically similar to the trifluoromethyl compounds while differing in electronic character.

4. Experimental

All air and moisture sensitive reactions were carried out in flame-dried or oven-dried (at 120 °C) glassware under an inert atmosphere of argon. All reactive liquids were transferred by syringe or cannula and were added into the flask through a rubber septum. All other solvents and reagents were used as received unless otherwise stated. Melting points were obtained on Mel-Temp metal block apparatus and are not corrected. ^1H and ^{13}C spectra were obtained on a Bruker 300 or 400 MHz spectrometer. All NMR spectra were obtained in a solution in $CDCl_3$. Chemical shifts (δ) are reported in parts per million (ppm). Multiplicities of signals in the ^1H spectra are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), etc. Infrared spectra were obtained on a Perkin-Elmer 1600 FR-IR spectrometer as liquid films or as a thin layer with NaCl cells. Intensities were reported as s (strong 67–100%), m (medium 34–66%), and w (weak 0–33%) with the following notations, br (broadened), sh (shoulder), etc. Optical rotations were recorded on JASCO, P-1100 model polarimeter (Japan Spectroscopic Co., Ltd) with sodium D line at the temperatures as indicated in the experimental for the specific compounds. Analytical Thin Lay Chromatography (TLC) was performed on Merck silica gel plates (Merck Kieselgel, 60, 0.25-mm thickness) with F_{254} indicator. Compounds were visualized under UV lamp and/or by developing with iodine, vanillin, (*p*)-anisaldehyde, $KMnO_4$, or phosphomolybdic acid followed by heating on a hot plate. FAB mass spectra were obtained using a VG70S double focusing magnetic sector mass spectrometer (VG Analytical, Manchester, UK, now Micromass/Waters) equipped with a Xe gas FAB gun (8 kV at 1.2 mA), an off-axis electron multiplier, and an MSS data system (MasCom, Bremen, Germany) at Johns Hopkins University. The resolution of the instrument was set at 10,000 (100 ppm peak width). Samples were mixed with *m*-nitrobenzyl-alcohol matrix deposited on the target of a direct insertion probe for introduction into the source. Nominal mass scan spectra were acquired with a mass scan range of 10–950 amu using a magnet scan rate of 25 s/dec. For accurate mass measurements, a narrower mass scan range was employed, with the matrix containing 10% PEG mass calibrant.

Iodides **(+)-6**[13] and **(+)-7**[11] were prepared according to Posner. Enantiomerically pure A-ring phosphine oxide **(−)-10** was prepared according to Posner.[13] Methyl trifluoromethyl sulfone was prepared according to Hendrickson.[14]

4.1. 25-SO_2–CF_3 C-8 TES-Protected alcohol (+)-8a

DMF (1 mL) was added to methyl trifluoromethyl sulfone (0.029 g, 0.190 mmol) in an oven-dried 10 mL pear-shaped bottom flask. This solution was added via cannula to a solution of sodium hydride (60% in mineral oil, 0.008 g, 0.211 mmol) in dimethylformamide (DMF) (0.5 mL) in a 10 mL oven-dried round bottom flask with a magnetic stirbar. The solution was stirred at room temperature for one hour at which time 23-iodide **(+)-6** (0.074 g, 0.160 mmol)

was added via cannula in DMF (1.5 mL). The reaction mixture was stirred for 16 h at which time TLC showed almost complete consumption of starting material. The reaction mixture was quenched with H_2O (2 mL) dropwise, then rinsed into a separatory funnel with ethyl acetate. The mixture was extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with ice water (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (90% hexanes/10% ethyl acetate), affording 0.034 g of 25-trifluoromethylsulfone **(+)-8a** as an oil in 45% yield. $[\alpha]_D$ +48.3 (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.02 (m, 1H), 3.22–3.09 (m, 2H), 2.03–1.91 (m, 2H), 1.85–1.34 (m, 11H), 1.23–1.20 (m, 3H), 1.13–1.00 (m, 3H), 0.96–0.89 (m, 15H), 0.57–0.51 (m, 6H). ^{19}F NMR (CCl_3F 300 MHz): δ −78.89. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 69.30, 56.24, 53.04, 50.04, 42.20, 40.74, 34.92, 34.60, 34.57, 27.31, 22.94, 18.32, 17.65, 17.46, 13.51, 6.94, 4.94. IR: 2961(s), 2886(s), 1446(m), 1421(w), 1362(s), 1212(s), 1186(s), 1161(w), 1120(s), 1086(m), 1061(w), 1011(m), 960(w), 952(w), 919(w), 910(w), 852(w), 818(w), 776(w), 743(m), 726(m). HRMS: calculated for $C_{22}H_{41}F_3O_3SSi$: 469.2420; found: 469.2438.

4.2. 16-ene 25-SO_2–CF_3 C-8 TES-Protected alcohol (+)-8b

DMF (1 mL) was added to methyl trifluoromethyl sulfone (0.009 g, 0.06 mmol) in an oven-dried 10 mL pear-shaped bottom flask. This solution was added via cannula to a solution of sodium hydride (0.002 g, 0.080 mmol) in DMF (0.5 mL) in a 10 mL oven-dried round bottom flask with a magnetic stirbar. The solution was stirred at room temperature for 1 h at which time 16-ene-23-iodide **(+)-7** (0.032 g, 0.070 mmol) was added via cannula in DMF (1.0 mL). The reaction mixture was stirred for 16 h at which time TLC showed almost complete consumption of starting material. The reaction mixture was quenched with H_2O (2.0 mL) dropwise, then rinsed into a separatory funnel with ethyl acetate. The mixture was extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with brine solution (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (90% hexanes/10% ethyl acetate), affording 0.023 g of 16-ene 25-trifluorosulfone **(+)-8b** in 82% yield. $[\alpha]_D$ +17.3 (*c* 1.4, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.28 (m, 1H), 4.11 (dd, 1H, J = 2.0 Hz), 3.19 (t, 2H, J = 8.0 Hz), 2.26 (m, 1H), 2.09 (m, 1H), 1.95–1.83 (m, 4H), 1.71–1.60 (m, 4H), 1.58–1.31 (m, 4H), 1.01 (d, 3H, J = 7.6 Hz), 1.00 (s, 3H), 0.95 (t, 9H, J = 8.0 Hz), 0.56 (q, 6H, J = 7.6 Hz). ^{19}F NMR (CCl_3F 300 MHz): δ −78.75. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 158.83, 120.64, 119.24(q), 68.86, 55.08, 49.80, 46.66, 35.75, 35.03, 34.86, 31.42, 30.73, 22.21, 18.97, 18.84, 18.01, 6.90, 4.90. IR: 2955(m), 2920(m), 2876(m), 1456(m), 1414(w), 1360(s), 1194(s), 1150(w), 1123(s), 1080(m), 1029(m), 972(w), 946(w), 924(w), 846(w). HRMS did not charge well for electrospray.

4.3. 25-SO_2–CF_3 C-8 Ketone (+)-9a

C-8 TBS-protected alcohol **(+)-8a** (0.034 g, 0.070 mmol) was dissolved in acetonitrile (5.0 mL) in an argon-purged 10 mL oven-dried round bottom flask equipped with a magnetic stir bar. After stirring for five minutes, HF (0.140 g, 7.00 mmol, 49% aqueous solution) was added at rt via syringe. The reaction mixture was stirred in the dark at rt for 3 h. TLC showed consumption of starting material. The reaction mixture was diluted with ethyl acetate (1.5 mL), and saturated $NaHCO_3$ was added until CO_2 liberation stopped. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (3× 10 mL). The combined extracts were washed with H_2O (1× 10 mL), brine (1× 10 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by column chromatography (80% hexanes/20% ethyl acetate) affording 17 mg of deprotected product as an oil in 71% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.06 (m, 1 H), 3.25–3.07 (m, 2H), 2.02–1.95 (m, 2H), 1.91–1.73 (m, 3H), 1.63–1.13 (m, 12H), 0.93 (d, 3H, J = 5.7 Hz), 0.92 (s, 3H).

C-8 alcohol (0.017 g, 0.050 mmol) was dissolved in methylene chloride (3.0 mL) in an oven-dried 10 mL round bottom flask with magnetic stir bar. PDC (0.045 g, 0.120 mmol) and Celite (0.045 g) were added and reaction mixture was stirred overnight. TLC showed consumption of starting material. Reaction mixture was charged directly onto a silica flash column (80% hexanes/20% ethyl acetate) for purification to afford 0.016 g of **(+)-9a** as an oil in 94% yield. $[\alpha]_D$ +8.72 (*c* 0.45, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.24–3.10 (m, 2H), 2.47–2.27 (m, 1H), 2.27–2.18 (m, 2H), 2.18–1.69 (m, 7H), 1.69–1.38 (m, 5H), 1.32–1.24 (m, 2H), 0.99 (d, 3H, J = 6.0Hz), 0.63 (s, 3H). ^{19}F NMR (CCl_3F 300MHz): δ −78.88. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 211.60, 61.83, 56.10, 49.91, 49.82, 40.90, 38.93, 35.22, 34.54, 27.51, 23.97, 19.05, 18.42, 17.51, 12.49. IR: 2953(m), 2887(m), 1714(s), 1539(w), 1463(w), 1454(m), 1380(s), 1295(w), 1195(s,sh), 1120(s), 1053(w), 952(w), 860(w), 801(w), 785(w), 693(w). HRMS: calculated for $C_{16}H_{25}F_3O_3S$: 354.1477; found: 354.1511.

4.4. 16-ene 25-SO_2–CF_3 C-8 Ketone (+)-9b

C-8 TBS-protected alcohol **(+)-8b** (0.028 g, 0.060 mmol) was dissolved in acetonitrile (5.0 mL) in an argon-purged 10 mL oven-dried round bottom flask equipped with a magnetic stir bar. After stirring for five minutes, HF (0.120 g, 5.97 mmol, 49% aqueous solution) was added at rt via syringe. The reaction mixture was stirred in the dark at room temperature for 3 h. TLC showed consumption of starting material. The reaction mixture was diluted with ethyl acetate (1.5 mL), and saturated $NaHCO_3$ was added until CO_2 liberation stopped. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (3× 10 mL). The combined extracts were washed with H_2O (1× 10 mL), brine (1× 10 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by column chromatography (80% hexanes/20% ethyl acetate) affording 0.018 g of deprotected product in 86% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.34 (m, 1H), 4.19 (m, 1H), 3.20 (t, 2H,

J = 8.0 Hz), 2.32–2.25 (m, 1H), 2.13–2.08 (m, 1H), 2.02–1.81 (m, 5H), 1.78–1.66 (m, 3H), 1.61–1.37 (m, 5H), 1.33 (d,6H, J = 6.8 Hz), 1.45–1.30 (m, 2H), 1.05 (s, 1H), 1.03 (d, 3H, J = 6.8 Hz).

C-8 alcohol (0.018 g, 0.051 mmol) was dissolved in methylene chloride (2.5 mL) in an oven-dried 10 mL round bottom flask with magnetic stir bar. PDC (0.045 g, 0.120 mmol) and Celite (0.045 g) were added and reaction mixture was stirred overnight. TLC showed consumption of starting material. Reaction mixture was charged directly onto a silica flash column (80% hexanes/20% ethyl acetate) for purification to afford 0.013 g of **(+)-4** in 72% yield. $[\alpha]_D$ +14.58 (c 0.06, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.32 (m, 1H), 3.20 (t, 2H, J = 8.0 Hz), 2.88–2.83 (m, 1H), 2.49–2.42 (m, 1H), 2.31–2.28 (m, 2H), 2.20–2.03 (m, 3H), 2.02–1.97 (m, 1H), 1.96–1.84 (m, 3H), 1.82–1.52 (m, 3H), 1.09 (d, 3H, J = 6.8 Hz), 0.81 (s, 3H). ^{19}F NMR (CCl_3F 300 MHz): δ −78.67. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 210.52, 156.56, 121.23, 119.40(q), 62.98, 53.67, 49.60, 40.41, 34.87, 34.35, 32.46, 27.07, 23.90, 21.56, 18.96, 17.33. IR: 3058(w), 2970(m), 2926(m), 2870(m), 1716(s), 1456(m), 1362(s), 1296(w), 1257(w), 1190(s), 1124(s), 1080(w), 1041(w), 986(w), 953(w), 892(w). HRMS: Did not charge well for electrospray.

4.5. (+)-AU-25-SO_2–CF_3 (+)-2

Enantiomerically pure phosphine oxide **(−)-10** (0.052 g, 0.089 mmol) was dissolved in THF (1.5 mL) in an oven-dried 10 mL round bottom flask with magnetic stir bar and purged with argon. Reaction vessel was cooled to −78 °C and n-BuLi (1.6 M) (0.063 mL, 0.100 mmol) was added dropwise resulting in a deep red color. After thirty minutes, ketone **(+)-9a** (0.016 g, 0.045 mmol) was dissolved in THF (1 mL), cooled to −78 °C, and added to the reaction mixture via cannula. Reaction mixture was stirred for 4 h at −78 °C at which time it was quenched at −78 °C by the addition of pH 7 buffer (5 mL) and allowed to come to room temperature. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by gradient column chromatography (80% hexanes/20% ethyl acetate to 50% hexanes/50% ethyl acetate) affording 0.018 g of trifluoromethylsulfone TBS-protected diol as an oil in 56% yield.

TBS-protected diol (0.018 g, 0.025 mmol) was dissolved in acetonitrile (1.0 mL) in an argon-purged 10 mL oven-dried round bottom flask equipped with a magnetic stir bar. After stirring for five minutes, HF (0.072 g, 3.60 mmol, 49% aqueous solution) was added at rt via syringe. The reaction mixture was stirred in the dark at rt for 2 h. TLC showed consumption of starting material. The reaction mixture was diluted with ether (1.5 mL), and saturated $NaHCO_3$ was added until CO_2 liberation stopped. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (4× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by flash silica gel chromatography (40% hexanes: 60% EtOAc) to afford **(+)-2** (0.008 g) as an oil in 67% yield. $[\alpha]_D$ +21.7 (c 0.30, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.35 (d, 1H, J = 11.2 Hz), 5.99 (d, 1H, J = 11.2 Hz), 5.31 (m,1H), 4.98 (s, 1H), 4.41 (m, 1H), 4.21 (m, 1H), 3.23–3.09 (m, 2H), 2.83–2.79 (m, 1H), 2.60–2.56 (m, 1H), 2.32–2.27 (m, 1H), 2.06–1.91 (m, 4H), 1.91–1.77 (m, 3H), 1.75–1.62 (m, 2H), 1.50–1.38 (m, 6H), 1.38–1.18 (m, 5H), 0.95 (d, 3H, J = 6.4 Hz), 0.53 (s, 3H). ^{19}F NMR (CCl_3F 300MHz): δ −78.77. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 147.65, 142.74, 133.12, 124.91, 117.23, 111.80, 75.77, 70.85,66.86, 56.24, 56.00, 45.90, 45.28, 42.89, 40.43, 35.79, 34.69, 29.02, 27.63, 23.51, 22.23, 18.53, 17.55, 12.00. IR: 3347(m, br), 2920(s), 2869(m), 2853(m), 1714(s), 1655(m), 1588(m), 1555(m), 1538(w), 1513(w), 1454(m), 1446(w), 1429(w), 1320(w), 1270(s), 1220(m), 1186(m), 1161(w), 1111(s), 1094(m), 1053(m), 1011(m), 868(w), 835(w), 793(w), 734(m). HRMS: calculated for $C_{25}H_{37}F_3O_4S$: 490.2365; found: 490.2363. UV (MeOH) λ_{max} = 263 nm (ε = 10,622).

^{13}C NMR did not detect the fluorinated carbon due to the small amount of sample. ^{19}F NMR confirms that this carbon is present.

4.6. AU-16-ene-25-SO_2–CF_3 (+)-3

Enantiomerically pure phosphine oxide **(−)-10** (0.050 g, 0.086 mmol) was dissolved in THF (1.5 mL) in an oven-dried 10 mL round bottom flask with magnetic stir bar and purged with argon. Reaction vessel was cooled to −78 °C and n-BuLi (1.6 M) (0.059 mL, 0.095 mmol) was added dropwise resulting in a deep red color. After thirty minutes, ketone **(+)-9b** (0.012 g, 0.034 mmol) was dissolved in THF (1 mL), cooled to −78 °C, and added to the reaction mixture via cannula. Reaction mixture was stirred for 5 h at −78 °C at which time it was quenched at −78 °C by the addition of pH 7 buffer (5 mL) and allowed to come to room temperature. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by gradient column chromatography (90% hexanes/10% ethyl acetate to 50% hexanes/50% ethyl acetate) affording 0.021 g of trifluoromethylsulfone TBS-protected diol in 88% yield.

TBS-protected diol (0.021 g, 0.029 mmol) was dissolved in acetonitrile (3.2 mL) in an argon-purged 10 mL oven-dried round bottom flask equipped with a magnetic stir bar. After stirring for five minutes, HF (0.058 g, 2.90 mmol, 49% aqueous solution) was added at rt via syringe. The reaction mixture was stirred in the dark at rt for 2 h. TLC showed consumption of starting material. The reaction mixture was diluted with ether (1.5 mL), and saturated $NaHCO_3$ was added until CO_2 liberation stopped. The reaction mixture was then rinsed

into a separatory funnel and extracted with ethyl acetate (4× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by flash silica gel chromatography (40% hexanes/60% EtOAc) to afford **(+)-3** (0.010 g) as an oil in 71% yield. $[\alpha]_D$ (+)5.66 (*c* 0.005, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ 6.37 (d, 1H, $J = 11.2$ Hz), 6.11 (d, 1H, $J = 10.8$ Hz), 5.34 (m,1H), 5.01 (s, 1H), 4.47–4.43 (m, 1H), 4.24 (m, 1H), 3.19(t, 2H, $J = 7.2$ Hz), 2.91–2.80 (m, 1H), 2.62–2.59 (m, 1H), 2.42–2.30 (m, 2H), 2.26–1.85 (m, 5H), 1.80–1.77 (m, 3H), 1.70–1.63 (m, 3H), 1.58–1.46 (m, 2H), 1.25–1.16 (m, 1H), 1.06 (d, 3H, $J = 6.8$ Hz), 0.68 (s, 3H). ^{19}F NMR (CCl_3F 300MHz): δ −79.01. ^{13}C NMR ($CDCl_3$ 100MHz): δ 158.25, 147.65, 142.03, 133.27, 124.78, 121.33, 117.07, 111.69, 70.69, 66.86, 58.31, 49.99, 49.71, 45.18, 42.87, 35.27, 34.90, 32.47, 29.40, 28.71, 23.52, 21.57, 18.83, 16.99. IR: 3340(m, br), 2954(m), 2931(s), 2875(m), 2852(m), 1594(m), 1445(m), 1398(m), 1358(s), 1296(w), 1193(s), 1115(s), 1044(m), 958(w), 910(w), 887(w). HRMS: calculated for $C_{25}H_{35}F_3O_4SNa^+$: 543.1999; found: 543.2024.The sample is oxidized in the mass spectrometer $M+O_2$. UV (MeOH) $\lambda_{max} = 259$ nm ($\varepsilon = 12{,}385$).

^{13}C NMR did not detect the fluorinated carbon due to the small amount of sample, but ^{19}F NMR confirms that this carbon is present.

4.7. 16-ene 25-SO_2–*n*-C_4F_9 C-8 TES-Protected alcohol

THF (4.0 mL) was added to commercially available perfluoro-methyl sulfone (**1**) (0.192 g, 0.645 mmol) in an oven-dried 10 mL round bottom flask with magnetic stirbar. The solution was cooled to −78 °C, and *n*-BuLi (1.5 M) (0.439 mL, 0.658 mmol) was added dropwise resulting in a slightly yellow solution. After stirring for 30 min, HMPA (0.40 mL) was added. After stirring for another 30 min, iodide **(+)-7** (0.058 g, 0.129 mmol), dissolved in THF (1.5 mL), was added via cannula. Reaction mixture was stirred at −50 °C overnight. TLC showed almost complete consumption of iodide **(+)-7**. The reaction mixture was quenched with H_2O (5.0 mL), then rinsed into a separatory funnel with ethyl acetate. The mixture was extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with brine solution (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (80% hexanes/20% diethyl ether), affording 0.076 g of 16-ene 25-sulfone in 95% yield. $[\alpha]_D$ +14.98 (*c* 1.35, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ 5.26 (s, 1H), 4.10 (s, 1H), 3.22 (t, 2H, $J = 10.4$ Hz), 2.29–2.21 (m, 1H), 2.09–1.83 (m, 5H), 1.70–1.24 (m, 8H), 1.01–0.91 (m, 15H), 0.59–0.51 (m, 6H). ^{13}C NMR ($CDCl_3$ 100 MHz): δ 158.87, 120.65, 118.54(t), 115.67(t), 114.45(t), 110.57(t), 68.90, 55.12, 51.25, 46.68, 35.78, 35.10, 34.88, 31.49, 30.74, 22.22, 18.82, 18.03, 6.87, 4.90. ^{19}F NMR ($CFCl_3$ 300 MHz): δ −81.20, −113.95, −121.83, −126.40. IR: 2959(m), 2913(m), 2875(m), 1594(w), 1456(w), 1368(m), 1317(w), 1292(w), 1242(s), 1223(s), 1204(s), 1166(m), 1141(s), 1116(m), 1084(m), 1028(m), 1009(m), 972(w), 940(w), 921(w), 871(w), 846(m), 808(m), 783(m), 732(m), 714(m). HRMS: calculated for $C_{25}H_{39}F_9O_3SSiNa^+$: 641.2138; found: 641.2119.

4.8. 16-ene 25-SO_2–*n*-C_4F_9 C-8 Ketone

C-8 TBS-protected alcohol (0.074 g, 0.120 mmol) was dissolved in acetonitrile (10.0 mL) in an argon-purged 10 mL oven-dried flask equipped with a magnetic stir bar. After stirring for five minutes, HF (0.540 mL, 13.0 mmol, 49% aqueous solution) was added at rt via syringe. The reaction mixture was stirred in the dark at rt for 1 h. TLC showed consumption of starting material. The reaction mixture was diluted with ether (5.0 mL), and saturated $NaHCO_3$ was added until CO_2 liberation stopped. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by column chromatography (80% hexanes/20% ethyl acetate) affording 0.040 g of deprotected product in 67% yield. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.33 (s, 1H), 4.18 (s, 1H), 3.24 (t, 2H, $J = 7.6$ Hz), 2.31–2.25 (m, 1H), 2.17–2.11 (m, 1H), 2.02–1.43 (m, 12H), 1.04 (s, 3H), 1.03 (d, 3H, $J = 7.2$ Hz).

C-8 alcohol (0.040 g, 0.080 mmol) was dissolved in methylene chloride (4.0 mL) in an oven-dried 10 mL round bottom flask with magnetic stirbar. PDC (0.072 g, 0.190 mmol) and Celite (0.072 g) were added and reaction mixture was stirred overnight. TLC showed consumption of starting material. Reaction mixture was charged directly onto a silica flash column (80% hexanes/20% ethyl acetate) for purification to afford 0.037 g of **(+)-4** in 93% yield. $[\alpha]_D$ +13.37 (*c* 0.9, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ 5.32 (s, 1H), 3.25 (m, 2H), 2,51–1.58 (m, 12H), 1.12–1.08 (m, 3H), 0.82 (s, 3H). ^{13}C NMR ($CDCl_3$ 100MHz): δ 210.55, 156.61, 121.27, 63.01, 53.66, 51.03, 40.42, 34.96, 34.35, 32.53, 27.08, 23.91, 21.57, 18.85, 17.33. ^{19}F NMR ($CFCl_3$ 300 MHz): δ −81.86, −114.60, −122.49, −127.07. IR: 2905(m), 2919(m), 2887(w), 2856(w), 1719(s), 1449(m), 1442(m), 1361(s), 1298(m), 1248(m), 1198(m), 1166(m), 1135(s), 1028(m), 990(w), 959(w), 871(w), 814(m), 796(w), 745(w), 720(m). HRMS: calculated for $C_{19}H_{23}F_9O_3SNa^+$: 525.1116; found: 525.1109.

The ^{13}C spectrum does not show fluorinated carbons due to an insufficient amount of sample. The fluorinated carbons are present according to the ^{19}F spectrum.

4.9. (+)-AU-16-ene 25-SO_2–*n*-C_4F_9 (+)-4

Enantiomerically pure phosphine oxide **(−)-10** (0.057 g, 0.098 mmol) was dissolved in THF (0.80 mL) in an oven-dried 10 mL round bottom flask with magnetic stir bar and purged with argon. Reaction vessel was cooled to −78 °C and *n*-BuLi (1.5 M) (0.065 mL, 0.098 mmol) was added dropwise resulting in a deep red color. After 30 min, ketone (0.016 g, 0.032 mmol) was dissolved in

THF (0.8 mL), cooled to −78 °C, and added to the reaction mixture via cannula. Reaction mixture was stirred for 3 h at −78 °C at which time it was quenched at −78 °C by the addition of pH 7 buffer (2.0 mL) and allowed to come to room temperature. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by column chromatography (90% hexanes/10% ethyl acetate) affording 0.008 g of perfluorosulfone**6** in 29% yield.

Perfluorosulfone **6** (0.008 g, 0.009 mmol) was dissolved in acetonitrile (1.0 mL) in an argon-purged 5 mL polypropylene vial equipped with a magnetic stir bar along with a cap. After stirring for five minutes, HF (0.020 g, 1.01 mmol, 49% aqueous solution) was added at rt via syringe. The reaction mixture was stirred in the dark at rt for 1.5 h. TLC showed consumption of starting material. The reaction mixture was diluted with ether (1.5 mL), and saturated $NaHCO_3$ was added until CO_2 liberation stopped. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (4× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by HPLC (15% 2-propanol in hexanes) to afford AU-16,-ene 25-SO_2–*n*-C_4F_9 (0.004 g) as an oil in 74% yield. $[\alpha]_D$ +4.03 (*c* 0.15, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ 6.32 (d, 1H, $J = 11.2$ Hz), 6.11 (d, 1H, $J = 11.2$ Hz), 5.34 (s, 2H), 5.01 (s, 1H), 4.45–4.43 (m, 1H), 4.25–4.22 (m, 1H), 3.23–2.97 (t, 2H, $J = 7.6$ Hz), 2.84–2.80 (m, 1H), 2.62–2.58 (m, 1H), 2.40–2.30 (m, 2H), 2.26–2.15 (m, 2H), 2.10–2.00 (m, 2H), 1.93–1.83 (m, 2H), 1.78–1.65 (m, 3H), 1.60–1.46 (m, 5H), 1.06 (d, 3H, $J = 6.8$ Hz), 0.68 (s, 3H). ^{19}F NMR ($CFCl_3$ 300MHz): δ −81.47, −114.27, −122.12, −126.71. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 158.25, 147.67, 142.01, 133.29, 14.76, 121.32, 117.06, 111.61, 70.64, 66.85, 58.31, 51.12, 49.98, 45.16, 42.87, 35.27, 34.95, 32.51, 29.40, 28.70, 23.52, 21.57, 18.68, 16.98. IR: 3375(m, br), 2963(m), 2930(s), 2858(m), 1642(w), 1551(w), 1499(w), 1361(s), 1230(s), 1211(m), 1159(w), 1139(m), 1120(w), 1059(m), 1039(m), 956(w), 877(w), 799(m), 766(m), 688(m), 669(m). HRMS: calculated for $C_{28}H_{35}F_9O_4SNa^+$: 661.2005; found: 661.2007. UV (MeOH) $\lambda_{max} = 265$ nm ($\varepsilon = 11{,}184$).

The ^{13}C spectrum does not show fluorinated carbons due to an insufficient amount of sample. The fluorinated carbons are present according to the ^{19}F spectrum.

4.10. 20-Keto-C-8 acetate (+)-12

C-8 TES-protected **(+)-11** (0.033 g, 0.106 mmol) was dissolved in CH_3CN (2 mL) in a 10 mL round bottom flask charged with a magnetic stir bar and an argon balloon. After stirring for five minutes, HF (0.430 mL, 10.6 mmol, 49% aqueous solution) was added at rt via syringe. The reaction mixture was stirred in the dark at rt for 1 hour. TLC showed consumption of starting material. The reaction mixture was diluted with ether (5.0 mL), and saturated $NaHCO_3$ was added until CO_2 liberation stopped. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was brought on to the next step without further purification. C-8 alcohol was dissolved in CH_2Cl_2 in an 10 mL oven-dried round bottom flask charged with argon and a magnetic stir bar. Pyridine (0.008 g, 0.23 mmol) and a catalytic amount of dimethylaminopyridine (0.001 g, 0.003 mmol) were added at 0 °C. After stirring for 15 min, acetic anhydride (0.021 g, 0.21 mmol) was added and the reaction mixture was stirred for 16 h allowing to come to room temperature. The reaction mixture was diluted with H_2O, extracted with methylene chloride (3× 30 mL), dried over magnesium sulfate, filtered, and concentrated. The acetate was purified by column chromatography (80% hexanes/20% ethyl acetate) affording 0.020 g (0.084mmol) of **(+)-12** in 80% overall yield. Data for **(+)-12** correlate with the literature.[12]

4.11. 3-Trifluoromethylsulfonyl-1-TMS-propanol (13)

3-Bromo-1-propanol (1.00 g, 7.2 mmol) was dissolved in 24 mL CH_2Cl_2 in a 50 mL oven-dried round bottom flask charged with argon and a magnetic stir bar. Trimethylsilylchloride (0.86 g, 7.92 mmol) was treated with triethylamine(0.80 g, 7.92 mmol) in 25 mL oven-dried pear-shaped flask. The eluent was transferred into the solution of 3-bromo-1-propanol via syringe and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with sodium bicarbonate, extracted with methylene chloride (3× 30 mL), dried over magnesium sulfate, filtered, and concentrated. The crude TMS-alcohol (1.50 g) as an oil was taken on to the next step.

TMS-protected 3-bromo-1-propanol (1.20 g, 5.7 mmol) was dissolved in dimethylacetamide (10 mL) and sodium trifluoromethyl sulfinate (1.20 g, 8.55 mmol) was added in a 25 mL oven-dried round bottom flask equipped with magnetic stir bar, argon balloon, and a reflux condenser. The solution was refluxed for 48 h. The reaction mixture was concentrated and crude NMR showed deprotected 3-trifluoromethylsulfonyl-1-propanol. The product was purified by flash silica gel chromatography (50% hexanes/50% ethyl acetate) to give 0.45 g of deprotected alcohol as an oil in 41% overall yield.

Alcohol (0.134 g, 0.700 mmol) was dissolved in 3 mL CH_2Cl_2 in a 25 mL oven-dried round bottom flask charged with argon and a magnetic stir bar. Trimethylsilylchloride (0.083 g, 0.770 mmol) was treated with triethylamine (0.078 g, 0.770 mmol) in 25 mL oven-dried pear-shaped flask. The eluent was transferred into the solution of alcohol via syringe and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with sodium bicarbonate, extracted with methylene chloride (3× 30 mL), dried over magnesium sulfate, filtered, and concentrated. The TMS-alcohol was purified

by kugelrohr at 160 °C to give TMS-alcohol **13** as a colorless oil in 70%yield. $[\alpha]_D$ −0.69 (*c* 1.0, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ 3.70 (t, 2H, J = 5.4 Hz), 3.33 (t, 2H, J = 11.1 Hz), 2.17–2.07 (m, 2H), 0.05 (s, 9H). ^{19}F NMR (CCl_3F 300MHz): δ −78.18. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 59.50, 46.73, 24.06, −0.900. IR: 2961(m), 2911(w), 2869(w), 1362(s), 1304(w), 1362(s), 1245(m), 1212(s), 1186(s), 1120(s), 1103(s), 944(m), 860(m), 843(s), 743(w), 693(w), 617(m). HRMS: sample did not charge for electrospray.

4.12. 20-epi-22-oxa-26-SO_2–CF_3-C-8 Acetate (−)-14

17-Keto-C-8 acetate **(+)-12** (0.020 g, 0.084 mmol) was dissolved in CH_2Cl_2 in a 10 mL oven-dried flask charged with argon and a magnetic stir bar. TMS-protected alcohol **13** (0.024 g, 0.092 mmol) was added and the solution was cooled to −78 °C. TMSOTf (0.019 g, 0.084 mmol) was added via syringe and the reaction mixture was stirred at −78 °C for 1 h. Triethylsilane(0.010 g, 0.084 mmol) was added via syringe and the reaction mixture was quickly brought to room temperature. After 5 h, the reaction was quenched by cautious addition of saturated sodium bicarbonate (2.0 mL). The mixture was diluted with H_2O (10 mL), extracted with CH_2Cl_2 (3× 10 mL), dried over magnesium sulfate, filtered, and concentrated. The product was purified by flash silica gel chromatography (50% hexanes/50% ethyl acetate) to give 0.020 g of 20-epi-22-oxa-26-trifluoromethylsulfone **(−)-14** as an oil in 57% yield. $[\alpha]_D$ −10.0 (*c* 0.10, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ 5.14 (m, 1H), 3.67–3.62 (m, 1H), 3.39–3.27 (m, 4H), 2.17–2.08 (m, 2H), 2.02 (s, 3H), 2.00–1.92 (m, 1H), 1.86–1.77 (m, 1H), 1.73–1.58 (m, 2H), 1.54–1.28 (m, 6H), 1.20–1.08 (m, 2H), 1.05 (d, 3H, J = 4.8 Hz), 0.86 (s, 3H). ^{19}F NMR (CCl_3F 300MHz): δ −78.90. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 170.77, 119.49(q), 78.15, 71.11, 64.56, 56.60, 50.89, 47.33, 41.85, 40.08, 30.62, 30.44, 24.65, 22.82, 22.14, 21.35, 18.08, 17.76, 17.67, 13.77. IR: 2944(m), 2869(m), 1730(s), 1447(w), 1364(s), 1239(s), 1214(s), 1189(s), 1156(m), 1115(s), 1056(m), 1015(m), 965(w), 932(w), 898(w), 862(w),765(m), 741(w), 708(w). HRMS: calculated for $C_{18}H_{29}F_3O_5S$: 413.1610; found: 413.1597.

4.13. 20-epi-22-oxa-26-SO_2–CF_3-C-8 Ketone (−)-15

C-8 acetate **(−)-14** (0.020 g, 0.048 mmol) was dissolved in THF (4.0 mL) in a 10mL oven-dried round bottom flask charged with a magnetic stir bar and argon balloon. The solution was cooled to −78 °C and DIBAL (1.5 M in THF, 0.100 mL, 0.145 mmol) was added dropwise via syringe. The solution was stirred for 16 h at −78 °C at which time the starting material was consumed. The reaction mixture was quenched with H_2O and extracted with ethyl acetate (3× 10 mL). The organics were dried over magnesium sulfate, filtered, and concentrated. The product was purified by flash silica gel chromatography (80% hexanes/20% ethyl acetate) to give 0.014 g of C-8 alcohol as a colorless oil in 83%yield.

C-8 alcohol (0.018 g, 0.051 mmol) was dissolved in methylene chloride (2.5 mL) in an oven-dried 10 mL round bottom flask with magnetic stir bar. PDC (0.036 g, 0.095 mmol) and Celite (0.036 g) were added and reaction mixture was stirred overnight. TLC showed consumption of starting material. Reaction mixture was charged directly onto a silica flash column (80% hexanes/20% ethyl acetate) for purification to afford 0.011 g of **(−)-15** in 80% yield. $[\alpha]_D$ −24.2 (*c* 0.50, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ 3.69 (m, 1H), 3.44–3.36 (m, 2H), 3.35–3.27 (m, 2H), 2.49 (m, 1H), 2.31–2.09 (m, 4H), 2.04–1.83 (m, 2H), 1.81–1.69 (m, 3H), 1.63–1.53 (m, 3H), 1.09 (d, 3H, J = 6.0 Hz), 0.64 (s, 3H). ^{19}F NMR (CCl_3F 300MHz): δ −78.85. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 211.65, 77.72, 64.67, 61.39, 56.69, 49.73, 47.22, 41.07, 39.08, 25.02, 24.01, 22.14, 19.35, 18.17, 13.16. IR: 2970(m), 2886(m), 1706(s), 1454(w), 1362(s), 1220(s), 1195(s), 1120(s), 1103(m), 1061(w), 768(s), 657(m). HRMS: calculated for $C_{16}H_{25}F_3O_4S$: 371.1504; found: 371.1498.

4.14. (−)-AU-20-epi-22-oxa-26-SO_2–CF_3 (−)-5

Enantiomerically pure A-ring-phosphine oxide **(−)-10** (0.060 g, 0.103 mmol) was dissolved in THF (1.5 mL) in an oven-dried 10 mL round bottom flask with magnetic stir bar and purged with argon. Reaction vessel was cooled to −78 °C and *n*-BuLi (1.6 M) (0.071 mL, 0.110 mmol) was added dropwise resulting in a deep red color. After 30 min, ketone **(−)-15** (0.015 g, 0.040 mmol) was dissolved in THF (1.0 mL), cooled to −78 °C, and added to the reaction via cannula. Reaction mixture was stirred for 3 h at −78 °C at which time it was quenched at −78 °C by the addition of pH 7 buffer (5.0 mL) and allowed to come to room temperature. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (3× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20 mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by gradient column chromatography (70% hexanes/30% ethyl acetate to 50% hexanes/50% ethyl acetate) affording 0.012 g of trifluoromethylsulfone TBS-protected diol as a colorless oil in 41% yield.

TBS-protected C-3 alcohol (0.010 g, 0.014 mmol) was dissolved in acetonitrile (1.5 mL) in an argon-purged 10 mL oven-dried round bottom flask equipped with a magnetic stir bar. After stirring for 5 min, HF (0.028 g, 1.4 mmol, 49% aqueous solution) was added at rt via syringe. The reaction mixture was stirred in the dark at rt for 2 h. TLC showed consumption of starting material. The reaction mixture was diluted with ether (1.5 mL), and saturated $NaHCO_3$ was added until CO_2 liberation stopped. The reaction mixture was then rinsed into a separatory funnel and extracted with ethyl acetate (4× 20 mL). The combined extracts were washed with H_2O (1× 20 mL), brine (1× 20mL) and dried over magnesium sulfate. The filtrate was concentrated in vacuo to give the crude product which was purified by flash silica gel chromatography (20% hexanes/80% EtOAc) to afford **(−)-5** (0.005 g) as an oil in 71% yield. $[\alpha]_D$ −36.0 (*c* 0.25, $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ 6.37 (d, 1H, J = 11.2 Hz), 6.00 (d, 1H, J = 10.8 Hz), 5.32 (m,1H),

4.99 (s, 1H), 4.44–4.41 (m, 1H), 4.24–4.21 (m, 1H), 3.68–3.63 (m, 1H), 3.42–3.25 (m, 4H), 2.85–2.74 (m, 1H), 2.63–2.55 (m, 1H), 2.33–2.29 (m, 1H), 2.21–2.11 (m, 2H), 2.05–1.99 (m, 2H), 1.96–1.85 (m, 2H), 1.77–1.63 (m, 3H), 1.60–1.47 (m, 6H), 1.39–1.21 (m, 1H), 1.17–1.08 (m, 1H), 1.07 (d, 3H, $J = 6.0$ Hz), 0.54 (s, 3H). ^{19}F NMR (CCl_3F 300 MHz): δ −78.23. ^{13}C NMR ($CDCl_3$ 100 MHz): δ 147.68, 142.81, 133.03, 124.93, 117.12, 111.75, 78.41, 70.84, 66.86, 64.67, 56.67, 55.78, 47.35, 45.76, 45.28, 42.90, 40.52, 29.06, 25.08, 23.41, 22.45, 22.13, 18.25, 12.75. IR: 3355(m, br), 2949(m), 2869(m), 1714(m), 1639(m), 1588(m), 1546(w), 1530(w), 1513(w), 1505(w), 1446(m), 1362(s), 1320(w), 1220(s), 1203(s), 1128(s), 1053(m), 969(w), 902(w), 860(w). HRMS: calculated for $C_{25}H_{37}F_3O_5S$: 506.2314; found: 506.2309. UV (MeOH) $\lambda_{max} = 263$ nm ($\varepsilon = 15{,}227$).

Acknowledgment

We thank the NIH (CA93547) for financial support.

References and notes

1. (a) Hess, A. F.; Weinstock, M.; Sherman, E. *J. Biol. Chem.* **1926**, *67*, 413–423; (b) Steenbock, H.; Black, A. J. *J. Biol. Chem.* **1924**, *61*, 405–422; (c) Steenbock, H.; Black, A. J. *J. Biol. Chem.* **1925**, *64*, 263–298.
2. Okamura, W. H.; Zhu, G. Vitamin D. Feldman, D., Editor-in-Chief; Academic Press: San Diego, 1997; pp 939–971.
3. (a) Posner, G. H.; Kahraman, M. Vitamin D. 2nd ed.; Feldman, D., Editor-in-Chief Academic Press: San Diego, 2003; (b) Posner, G. H.; Kahraman, M. *Eur. J. Org. Chem.* **2003**, *20*, 3889–3895.
4. Yamada, S.; Shimizu, M.; Yamamoto, K. *Med. Res. Rev.* **2003**, *23*, 89–115.
5. Kirsch, Peer *Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004, pp 8–16, 237–243.
6. Maienfisch, P.; Hall, R. G. *Chimia* **2004**, *58*, 93–99.
7. Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing: Oxford, 2004, pp 1–7.
8. Uneyama, K. *Organofluorine Chemistry*; Balckwell Publishing: Oxford, 2006, pp 6–15, 81–82, 173–180, 206–215.
9. Munker, R.; Kobayashi, T.; Elstner, E.; Norman, A. W.; Uskokovic, M.; Zhang, W.; Andreeff, M.; Koeffler, H. P. *Blood* **1996**, *88*, 2201–2209; (b) Stern, P. S.; Mavreas, T.; Tanaka, Y.; DeLuca, H. F.; Ikekawa, N.; Kobayashi, Y. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 9–13; (c) Inaba, M.; Okuno, S.; Nishizawa, Y.; Yukioka, K.; Otani, S.; Matsui-Yuasa, I.; Wa, S. M.; DeLuca, H. F.; Morii, H. *Arch. Biochem. Biophys.* **1987**, *258*, 421–425.
10. Mehta, R. G.; Mehta, R. R. *J. Nutr. Biochem.* **2002**, *13*, 252–264.
11. Posner, G. H.; Wang, Q.; Han, G.; Lee, J.; Crawford, K.; Zand, S.; Brem, H.; Peleg, S.; Dolan, P.; Kenslar, T. W. *J. Med. Chem.* **1999**, *42*, 3425–3435.
12. Posner, G. H.; Crawford, K. R.; Sui-Caldera, M.; Reddy, S.; Sarabia, S. F.; Feldman, D.; van Etten, E.; Mathieu, C.; Gennaro, L.; Vuoros, P.; Peleg, S.; Dolan, P.; Kenslar, T. W. *J. Med. Chem.* **2000**, *43*, 3581–3586.
13. Dai, H.; Posner, G. H. *Synthesis* **1994**, 1383–1398.
14. Methyl-trifluoromethyl sulfone was prepared according to: Hendrickson, J. B.; Skipper, P. L. *Tetrahedron* **1976**, *32*, 1627.
15. Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. *J. Med. Chem.* **1992**, *35*, 3280–3287.
16. (a) Reddy, G. S.; Clark, J. W.; Tserng, K.; Uskokovic, M. R.; McLane, J. A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1879–1884; (b) Uskokovic, M. R.; Studzinski, G. P.; Gardner, J. P.; Reddy, S. G.; Campbell, M. J.; Koeffler, H. P. *Curr. Pharm. Des.* **1997**, *3*, 99–123.