Published in final edited form as:

Bioorg Med Chem. 2007 August 15; 15(16): 5509–5518. doi:10.1016/j.bmc.2007.05.051.

Antiproliferative, Low-calcemic, Fluorinated Sulfone Analogs of 1 α ,25-Dihydroxyvitamin D₃: Chemical Synthesis and Biological Evaluation

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

^aDepartment of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, Maryland 21218.

^bDivision of Toxicology, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, Maryland 21205.

Abstract

Novel fluorinated sulfone analogs of the hormone 1 α ,25-dihydroxyvitamin D₃ 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 1 α ,25-dihydroxyvitamin D₃ 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.

Introduction

The hormone 1 α ,25-dihydroxyvitamin D₃, more commonly known as calcitriol (**1**) (Figure 1), has been recognized to be essential to human health for many decades. First discovered as a treatment for the disease rickets in late eighteenth 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 D₃ 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 pathway³ to avoid degradation, and increasing the interactions between the vitamin D receptor (VDR)^{3a,4} and the hormone, 1 α ,25-dihydroxyvitamin D₃ (**1**). One modification of 1 α ,25-dihydroxyvitamin D₃ (**1**) that considers all of these approaches is the incorporation of one or more fluorine atoms.

Correspondence to: Gary H. Posner, ghp@jhu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 hydrogen⁶⁻⁸ 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 D₃ analog design and synthesis.

There are several instances of incorporation of fluorine into the vitamin D₃ structure⁹ 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 D₃ 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-*t*-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 *t*-butyl sulfone analogs, we prepared a series of fluorinated compounds.

Results and Discussion

Chemistry

Synthesis of analogs (+)-**AU-25-SO₂-CF₃** (**2**), and (+)-**AU-16-ene-25-SO₂-CF₃** (**3**), outlined in scheme 1, begins with previously reported 22-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-ring¹³ (–)-**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-SO₂-CF₃ 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 etherification¹² with C-18 ketone (+)-**12** to give 20-*epi*-22-oxa-27-SO₂-CF₃ (–)-**14**. The 20-*epi* configuration was confirmed by a ¹H NMR upfield shift of the 21-methyl group from approximately 0.68 ppm 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 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-SO₂-CF₃** (**5**).

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**) (Figure 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 (Figure 2). With this exciting result, we designed nonafluorobutylsulfone **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 D₃ analogs^{9,10} indicate that more than three fluorine atoms may create a more biologically active compound. However, the C₄F₉ 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 nonafluoro-compound might result from too many fluorine atoms making the molecule too lipophilic and 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-*t*-butyl sulfone which displays high antiproliferative activity.¹² Terminally fluorinated analog **5** shows excellent antiproliferative activity even at 3–7 nM concentrations (Figure 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 D₃ (**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 (Figure 3).

Conclusion

In conclusion, we have shown, for the first time, that fluorination of the 26 or 27 position of 1α,25-vitamin D₃ 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 *t*-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 *t*-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.

Experimental Section

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 ¹³C spectra were obtained on

a Bruker 300 or 400 MHz spectrometer. All NMR spectra were obtained in a solution in CDCl₃. 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 Layer Chromatography (TLC) was performed on Merck silica gel plates (Merck Kieselgel, 60, 0.25-mm thickness) with F₂₅₄ indicator. Compounds were visualized under UV lamp and/or by developing with iodine, vanillin, (p)-anisaldehyde, KMnO₄, 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 (8kV @ 1.2mA), 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 (100ppm 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 sec/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

25-SO₂-CF₃ 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 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 stirred 16 hours at which time TLC showed almost complete consumption of starting material. The reaction was quenched with H₂O (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. [α]_D = +48.3 (*c*=1.0, CHCl₃) ¹H NMR (CDCl₃, 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). ¹⁹F NMR (CCl₃F 300MHz): δ –78.89. ¹³C NMR (CDCl₃ 100MHz): 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 C₂₂H₄₁F₃O₃SSi: 469.2420; found: 469.2438.

16-ene 25-SO₂-CF₃ 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 stirred at room temperature for one hour 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 stirred 16 hours at which time TLC showed almost complete consumption of starting material. The reaction was quenched with H₂O (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. $[\alpha]_D^{25} = +17.3$ (c=1.4, CHCl₃) ¹H NMR (CDCl₃, 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). ¹⁹F NMR (CCl₃F 300MHz): δ -78.75. ¹³C NMR (CDCl₃ 100MHz): 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.

25-SO₂-CF₃ 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 hours. TLC showed consumption of starting material. The reaction was diluted with ethyl acetate (1.5 mL), and saturated NaHCO₃ was added until CO₂ 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 H₂O (1×10 mL), brine (1×10mL), 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. ¹H NMR (CDCl₃, 400 MHz): δ 4.06 (m, 1H), 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 (3.0mL) 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 stirred overnight. TLC showed consumption of starting material. Reaction mixture 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. $[\alpha]_D^{25} = +8.72$ (c=0.45, CHCl₃) ¹H NMR (CDCl₃, 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). ¹⁹F NMR (CCl₃F 300MHz): δ -78.88. ¹³C NMR (CDCl₃ 100MHz): 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 C₁₆H₂₅F₃O₃S: 354.1477; found: 354.1511.

16-ene 25-SO₂-CF₃ 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 hours. TLC showed consumption of starting material. The reaction was diluted with ethyl acetate (1.5 mL), and saturated NaHCO₃ was added until CO₂ 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 H₂O (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. ¹H NMR (CDCl₃, 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 stirred overnight. TLC showed consumption of starting material. Reaction mixture charged directly onto a silica flash column (80% hexanes/20% ethyl acetate) for purification to afford 0.013 g of (+)-**4** in 72% yield. [α]_D = +14.58 (c=0.06, CHCl₃) ¹H NMR (CDCl₃, 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). ¹⁹F NMR (CCl₃F 300MHz): δ -78.67. ¹³C NMR (CDCl₃ 100MHz): 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.

(+)-AU-25-SO₂-CF₃ (+)-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** (0.016g, 0.045 mmol) was dissolved in THF (1 mL), cooled to –78°C, and added to the reaction *via* cannula. Reaction stirred for 4 hours 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 H₂O (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 (1.0mL) 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 hours. TLC showed consumption of starting material. The reaction was diluted with ether (1.5 mL), and saturated NaHCO₃ was added until CO₂ 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 H₂O (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 chromatography (40% Hexanes: 60% EtOAc) to afford (+)-**2** (0.008 g) as an oil in 67% yield. [α]_D = +21.7 (c=0.30, CHCl₃) ¹H NMR (CDCl₃, 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). ¹⁹F NMR (CCl₃F 300MHz): δ -78.77. ¹³C NMR (CDCl₃ 100MHz): 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) $\lambda_{\max}$ = 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.

AU-16-ene-25-SO₂-CF₃ (+)-3

Enantiomerically pure phosphine oxide (–)-**10** (0.050g, 0.086 mmol) was dissolved in THF (1.5ml) 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 *via* cannula. Reaction stirred for 5 hours 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 H₂O (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 (3.2mL) 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 hours. TLC showed consumption of starting material. The reaction was diluted with ether (1.5 mL), and saturated NaHCO₃ was added until CO₂ 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 H₂O (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 chromatography (40% Hexanes: 60% EtOAc) to afford (+)-**3** (0.010 g) as an oil in 71% yield. $[\alpha]_D^{25}$ = +5.66 (c = 0.005, CHCl₃) 1H NMR (CDCl₃, 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 (CCl₃F 300MHz): δ –79.01. ^{13}C NMR (CDCl₃ 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 (ϵ = 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.

16-ene 25-SO₂-*n*C₄F₉ 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 (1.5M) (0.439 ml, 0.658 mmol) was added dropwise resulting

in a slightly yellow solution. After stirring 30 minutes, HMPA (0.40 mL) was added. After stirring another 30 minutes, iodide (+)-**7** (0.058 g, 0.129 mmol), dissolved in THF (1.5 mL), was added *via* cannula. Reaction stirred at -50°C overnight. TLC showed almost complete consumption of iodide (+)-**7**. The reaction 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. $[\alpha]_{\text{D}} = +14.98$ ($c = 1.35$, 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 100MHz): 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 300MHz): 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 $\text{C}_{25}\text{H}_{39}\text{F}_9\text{O}_3\text{SSiNa}^+$: 641.2138; found: 641.2119.

16-ene 25- SO_2 - $n\text{C}_4\text{F}_9$ 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 hour. TLC showed consumption of starting material. The reaction 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 stir bar. PDC (0.072 g, 0.190 mmol) and celite (0.072 g) were added and reaction stirred overnight. TLC showed consumption of starting material. Reaction mixture charged directly onto a silica flash column (80% hexanes/20% ethyl acetate) for purification to afford 0.037 g of (+)-**4** in 93% yield. $[\alpha]_{\text{D}} = +13.37$ ($c = 0.9$, 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 300MHz): 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 $\text{C}_{19}\text{H}_{23}\text{F}_9\text{O}_3\text{SNa}^+$: 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.

(+)-AU-16-ene 25- SO_2 - $n\text{C}_4\text{F}_9$ (+)-**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 $n\text{BuLi}$ (1.5 M) (0.065 mL, 0.098 mmol) was

added dropwise resulting in a deep red color. After thirty minutes, ketone (0.016 g, 0.032 mmol) was dissolved in THF (0.8 mL), cooled to -78°C , and added to the reaction *via* cannula. Reaction stirred for 3 hours 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 hours. TLC showed consumption of starting material. The reaction 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- $\text{SO}_2\text{-}n\text{C}_4\text{F}_9$ (0.004 g) as an oil in 74% yield. $[\alpha]_{\text{D}}^{25} = +4.03$ ($c = 0.15$, 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_3 300 MHz): 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 $\text{C}_{28}\text{H}_{35}\text{F}_9\text{O}_4\text{SNa}^+$: 661.2005; found: 661.2007. UV (MeOH) $\lambda_{\text{max}} = 265$ nm ($\epsilon = 11,184$).

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.

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 roundbottom 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 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 a 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 minutes, acetic anhydride (0.021 g, 0.21 mmol) was added and the reaction stirred 16 hours coming to room temperature. The reaction was diluted with H_2O , extracted with methylene chloride (3×30 mL), dried over magnesium sulfate, filtered, and concentrated. The acetate was

purified column chromatography (80% hexanes/20% ethyl acetate) affording 0.020 g (0.084mmol) of (+)-**12** in 80% overall yield. Data for (+)-**12** correlates with literature.¹²

3-Trifluoromethylsulfonyl-1-TMS-propanol **13**

3-Bromo-1-propanol (1.00 g, 7.2 mmol) was dissolved in 24 mL CH₂Cl₂ in a 50mL oven-dried round bottom 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 stirred 1 hour. The reaction 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 25mL oven-dried round bottom flask equipped with magnetic stir bar, argon balloon, and a reflux condenser. The solution was refluxed for 48 hours. The reaction was concentrated and crude NMR showed deprotected 3-trifluoromethylsulfonyl-1-propanol. The product was purified by flash silica 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 CH₂Cl₂ in a 25mL oven-dried round bottom 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 stirred 1 hour. The reaction 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. [α]_D = -0.69 (c=1.0, CHCl₃) ¹H NMR (CDCl₃, 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). ¹⁹F NMR (CCl₃F 300MHz): δ -78.18. ¹³C NMR (CDCl₃ 100MHz): 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.

20-epi-22-oxa-26-SO₂-CF₃-C-8 acetate (-)-**14**

17-keto-C-8 acetate (+)-**12** (0.020 g, 0.084 mmol) was dissolved in CH₂Cl₂ 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 stirred at -78°C for 1 hour Triethylsilane(0.010 g, 0.084 mmol) was added via syringe and the reaction mixture was quickly brought to room temperature. After 5 hours, the reaction was quenched by cautious addition of saturated sodium bicarbonate (2.0 mL). The mixture was diluted with H₂O (10 mL), extracted with CH₂Cl₂ (3×10 mL), dried over magnesium sulfate, filtered and concentrated. The product was purified by flash silica 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. [α]_D = -10.0 (c=0.10, CHCl₃) ¹H NMR (CDCl₃, 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). ¹⁹F NMR (CCl₃F 300MHz): δ -78.90. ¹³C NMR (CDCl₃ 100MHz): 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 C₁₈H₂₉F₃O₅S: 413.1610; found: 413.1597.

20-epi-22-oxa-26-SO₂-CF₃-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 charged with a magnetic stir bar and argon balloon. The solution was cooled to –78°C and DIBAL (1.5M in THF, 0.100 mL, 0.145 mmol) was added dropwise *via* syringe. The solution stirred 16 hours at –78°C at which time the starting material was consumed. The reaction was quenched with H₂O 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 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 stirred overnight. TLC showed consumption of starting material. Reaction mixture 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, CHCl₃) ¹H NMR (CDCl₃, 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). ¹⁹F NMR (CCl₃F 300MHz): δ –78.85. ¹³C NMR (CDCl₃ 100MHz): 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 C₁₆H₂₅F₃O₄S: 371.1504; found: 371.1498.

(–)-AU-20-epi-22-oxa-26-SO₂-CF₃ (–)-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 thirty minutes, 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 stirred for 3 hours 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 H₂O (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 five minutes, 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 hours. TLC showed consumption of starting material. The reaction was diluted with ether (1.5 mL), and saturated NaHCO₃ was added until CO₂ 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 H₂O (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 chromatography (20% Hexanes: 80% EtOAc) to afford (–)-5 (0.005g) as an oil in 71% yield. $[\alpha]_D = -36.0$ (c=0.25, CHCl₃) ¹H NMR (CDCl₃, 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 300MHz): δ -78.23. ^{13}C NMR (CDCl_3 100MHz): 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 $\text{C}_{25}\text{H}_{37}\text{F}_3\text{O}_5\text{S}$: 506.2314; found: 506.2309. UV (MeOH) λ_{max} =263 nm (ϵ = 15,227).

Acknowledgments

We thank the NIH (CA93547) for financial support.

References

1. a Hess AF, Weinstock M, Sherman E. J. Biol. Chem 1926;67:413–423. b Steenbock H, Black AJ. J. Biol. Chem 1924;61:405–422. c Steenbock H, Black AJ. J. Biol. Chem 1925;64:263–298.
2. Okamura, WH.; Zhu, G. Vitamin D. San Diego: Feldman D., Editor-in-Chief; Academic Press; 1997. p. 939-971.
3. Posner, GH.; Kahraman, M. Vitamin D. 2nd Ed.. San Diego: Feldman, D., Editor-in-Chief Academic Press; 2003. b Posner GH, Kahraman M. Eur. J. Org. Chem 2003;20:3889–3895.
4. Yamada S, Shimizu M, Yamamoto K. Med. Res. Rev 2003;23:89–115. [PubMed: 12424754]
5. Kirsch, Peer. Modern Fluoroorganic Chemistry. Synthesis, Reactivity, Applications. Weinheim: Wiley-VCH; 2004. p. 8-16.p. 237-243.
6. Maienfisch P, Hall RG. Chimia 2004;58:93–99.
7. Chambers, RD. Fluorine in Organic Chemistry. Oxford: Blackwell Publishing; 2004. p. 1-7.
8. Uneyama, K. Organofluorine Chemistry. Oxford: Balckwell Publishing; 2006. p. 6-15.p. 81-82.p. 173-180.p. 206-215.
9. a Munker R, Kobayashi T, Elstner E, Norman AW, Uskokovic M, Zhang W, Andreeff M, Koeffler HP. Blood 1996;88:2201–2209. [PubMed: 8822940] b Stern PS, Mavreas T, Tanaka Y, DeLuca HF, Ikekawa N, Kobayashi Y. J. Pharmacol. Exp. Ther 1984;229:9–13. [PubMed: 6323693] c Inaba M, Okuno S, Nishizawa Y, Yukioka K, Otani S, Matsui-Yuasa I, Wa SM, DeLuca HF, Morii H. Arch. Biochem. Biophys 1987;258:421–425. [PubMed: 2823715]
10. Mehta RG, Mehta RR. J. Nutr. Biochem 2002;13:252–264. [PubMed: 12015155]
11. Posner GH, Wang Q, Han G, Lee J, Crawford K, Zand S, Brem H, Peleg S, Dolan P, Kenslar TW. J. Med. Chem 1999;42:3425–3435. [PubMed: 10479276]
12. Posner GH, Crawford KR, Sui-Caldera M, Reddy S, Sarabia SF, Feldman D, van Etten E, Mathieu C, Gennaro L, Vuoros P, Peleg S, Dolan P, Kenslar TW. J. Med. Chem 2000;43:3581–3586. [PubMed: 11000014]
13. Dai H, Posner GH. Synthesis 1994:1393–1398.
14. Methyl-trifluoromethyl sulfone was prepared according to Hendrickson JB, Skipper PL. Tetrahedron 1976;32:1627.
15. Posner GH, Nelson TD, Guyton KZ, Kensler TW. J. Med. Chem 1992;35:3280–3287. [PubMed: 1324319]
16. a Reddy GS, Clark JW, Tserng K, Uskokovic MR, McLane JA. Bioorg. Med. Chem. Lett 1993;3:1879–1884. b Uskokovic MR, Studzinski GP, Gardner JP, Reddy SG, Campbell MJ, Koeffler HP. Curr. Pharm. Des 1997;3:99–123.

Figure 1.

Figure 2.

Figure 3.

Scheme 1.

Scheme 2.