Potent, Selective and Low-Calcemic Inhibitors of CYP24 Hydroxylase: 24-Sulfoximine Analogues of the Hormone 1α,25-Dihydroxyvitamin D_3

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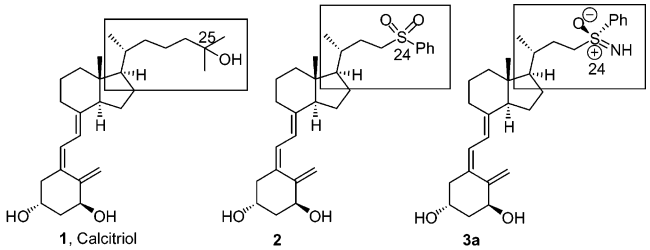
A dozen 24-sulfoximine analogues of the hormone 1α,25-dihydroxyvitamin D_3 were prepared, differing not only at the stereogenic sulfoximine stereocenter but also at the A-ring. Although these sulfoximines were not active transcriptionally and were only very weakly antiproliferative, some of them are powerful hydroxylase enzyme inhibitors. Specifically, 24-(*S*)-NH phenyl sulfoximine **3a** is an extremely potent CYP24 inhibitor (IC_{50} = 7.4 nM) having low calcemic activity. In addition, this compound shows high selectivity toward the CYP24 enzyme in comparison to CYP27A1 (IC_{50} > 1000 nM) and CYP27B (IC_{50} = 554 nM).

Introduction

Medicinal chemists are designing analogues to be at least as potent as, but less calcemic than, the natural hormone 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**) for chemotherapy of diverse human illnesses.[1−3] We have shown that some new vitamin D analogues, even though lacking the classical side-chain terminal OH group, are transcriptionally active and low-calcemic.[4,5] Among such new analogues characterized by a 24-sulfone functional group, 24-sulfone **2** stands out as being a very potent (IC_{50} = 28 nM), low-calcemic, and selective inhibitor of the human cyctochrome P450C24 (CYP24) hydroxylase enzyme responsible for the main catabolism of calcitriol (**1**).[6] Therefore, surrogates for the sulfone functional group were considered. Now we report on a new series of 24-sulfoximines **3a**−**3l** in which the traditional side-chain terminal OH group is lacking but is replaced by a sulfoximine NH group.



Chemistry

Sulfoximines,[7] the monoimino analogues of sulfones, have gained considerable attention in synthetic organic chemistry, not only due to their high stability toward racemization but also due to their remarkable biological activities.[8] As part of an ongoing program of research into design and synthesis of potent and low-calcemic analogues of **1**, we have prepared a range of 24-sulfoximine analogues of the natural hormone as outlined in Schemes 1−4. The 22-iodide (+)-**4**[9] underwent iodide substitution by the required *N*-*tert*-butyldimethylsilyl-protected sulfoximines[10] followed by bisdesilylation to form C,D-ring side-chain NH-sulfoximines **6** as C-8 secondary alcohols. Oxidation at C-8 produced the corresponding C-8 ketones **7** (Scheme 1, Table 1). Horner−Wadsworth−Emmons (HWE) coupling of ketones **7** with A-ring phosphine oxide **8** conjugate base, followed by HF-promoted desilylation, generated the target sulfoximine analogues **3a**−**3g** in good yields (Scheme 2, Table 2). When racemic A-ring **8** (where R_3, R_3 = CH_2 and R_4 = OTBS; Table 2, entries 1 and 2) was used in the HWE coupling reaction, the reaction afforded a diastereomeric pair of products, **3** and **3′**, that were separated on a semipreparative chiral HPLC column. Each of these diastereomers was characterized fully and distinguished from its partner by analogy to our 24-sulfone analogues.[6] When enantiomerically pure 19-nor (where R_3, R_3 = H, H and R_4 = OTBS; Table 2, entries 3 and 4) and 1-deoxy (where R_3, R_3 = CH_2 and R_4 = H; Table 2, entry 5) A-rings were used in the aforementioned coupling reaction, 24-NH-phenyl sulfoximines were obtained in good yields after desilylation with HF in acetonitrile at room temperature.

The preparation of 4-fluorophenyl sulfoximine analogues **3h** and **3i** is outlined in Scheme 3. The first step is a replacement of the iodide in building block 22-iodide (+)-**9**[11] with racemic sulfoximine (±)-**10** followed by desilylation to form para-fluorinated phenyl sulfoximine analogues **3h** and **3i** as an approximately 1:1 diastereomeric mixture in 46% overall yield. This mixture was also separated on a semipreparative chiral HPLC column, and diastereomers were distinguished from each other by ^1H and ^{13}C NMR spectroscopy correlation with some of the other sulfoximines described here. The

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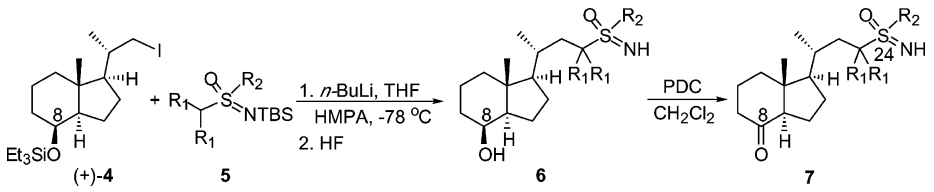
Scheme 1



Scheme 2

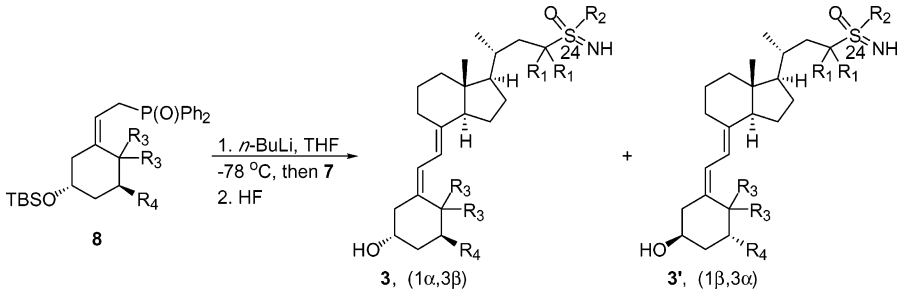


Table 1. Synthesis of C,D-Ring Ketones **7**

entry	configuration of sulfoximine (**5**)	R_1, R_1	R_2	**6** (yield %)[a]	**7** (yield %)[a]
1	(+)-(*S*)	H, H	Ph	**6a**, 53	**7a**, 95
2	(−)-(*R*)	H, H	Ph	**6b**, 64	**7b**, 96
3	(±)-(*R*/*S*)	-$(CH_2)_2$-	Ph	**6c**, 73	**7c**, 85

[a] Isolated yields.

Table 2. Synthesis of Sulfoximine Analogues **3**

entry	configuration of sulfoximine	R_1, R_1	R_2	R_3	R_4	**3** + **3′** (yield %)[a]
1	(+)-(*S*)	H, H	Ph	$=CH_2$	OH	47
2	(−)-(*R*)	H, H	Ph	$=CH_2$	OH	44
3	(−)-(*R*)	H, H	Ph	H, H	OH	55[b]
4	(+)-(*S*)	H, H	Ph	H, H	OH	23[b]
5	(+)-(*S*)	H, H	Ph	$=CH_2$	H	68[b]
6	(±)-(*R*/*S*)	-$(CH_2)_2$-	Ph	$=CH_2$	OH	40[b]

[a] Isolated yields for two steps. [b] Enantiomerically pure A-rings were used.

MK notation for products **3a**−**3j** refers to the initials of the researcher who prepared these sulfoximines.

To alter C,D-ring side-chain conformation as well as to slow side-chain catabolism, 22-ene analogues **3j**−**3l** were synthesized as shown in Scheme 4. The Horner−Wittig reaction of the building block 22-aldehyde (+)-**12**[12] with α-fluoro N-silylated sulfoximine (*S*)-**13**, followed by deprotection resulted in olefinic sulfoximine **3j** as a single geometrical isomer (see Scheme 4) about the C22−C23 double bond in overall 52% yield. Similarly, the reaction of the *N*-silylated diethylphosphonomethyl sulfoximine (*S*)-**14** afforded olefinic analogues **3k** and **3l** in a 2:1 ratio, in overall 56% yield. Under the same reaction conditions, analogue **3l** also was obtained as a C-20 epi isomer whose structure was tentatively assigned by analogy to closely related C-20 epi compounds.[13] The SS notation for products **3k**−**3l** refers to the initials of the researcher who prepared these sulfoximines.

Biology Results and Discussion

The in vitro antiproliferative potencies of 24-NH sulfoximine analogues **3a**−**3l** and calcitriol (**1**) were determined by our standard murine keratinocyte assay.[14] However, none of the sulfoximine analogues **3** was strongly antiproliferative (data not shown).

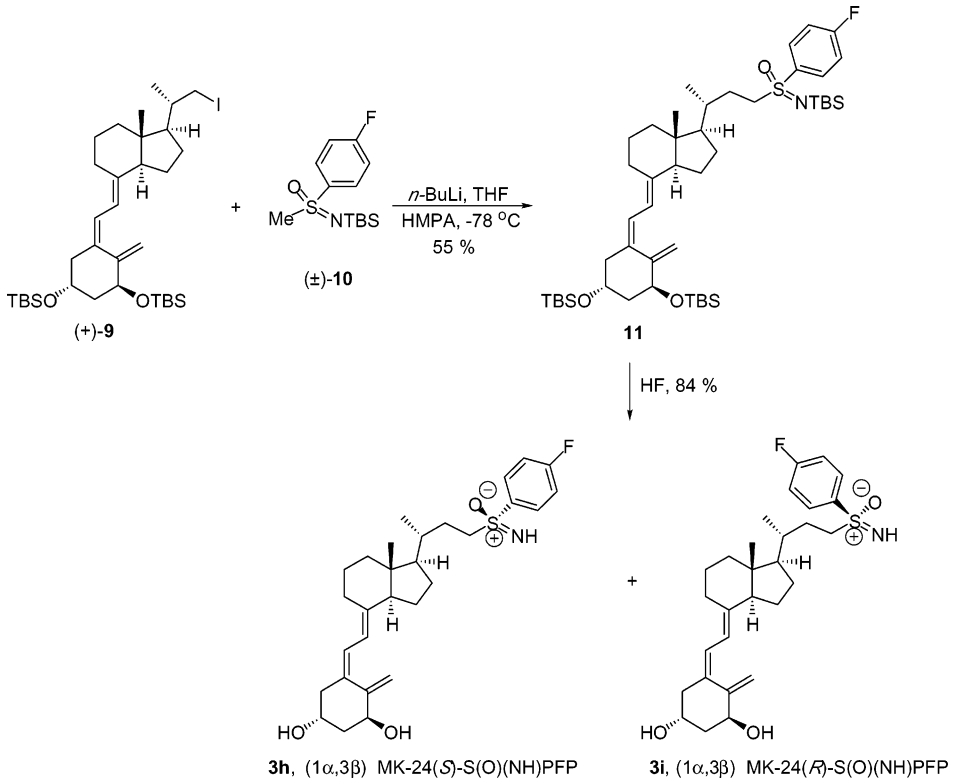
By use of a standard protocol,[15] VDR-mediated in vitro transcriptional activities of some of the sulfoximine analogues were tested in CV-1 cells cotransfected with the recombinant human VDR plasmid and the osteocalcin VDRE attached to the thymidine kinase promoter−growth hormone reporter. Sulfoximines **3a** and **3b** were found to be significantly less potent (ED_{50} = >1 μM) than calcitriol (**1**, ED_{50} = 0.4 nM) (data not shown).

As a measure of toxicity and safety in animals,[4,15] each of the sulfoximine analogues **3a**, **3d**, and **3e** was administered orally to rats daily for 1 week at a 20-fold higher dose (10 μg/kg of body weight) than calcitriol (**1**, 0.5 μg/kg of body weight). None of the sulfoximines significantly elevated the levels of calcium in the blood of rats (Figure 1).

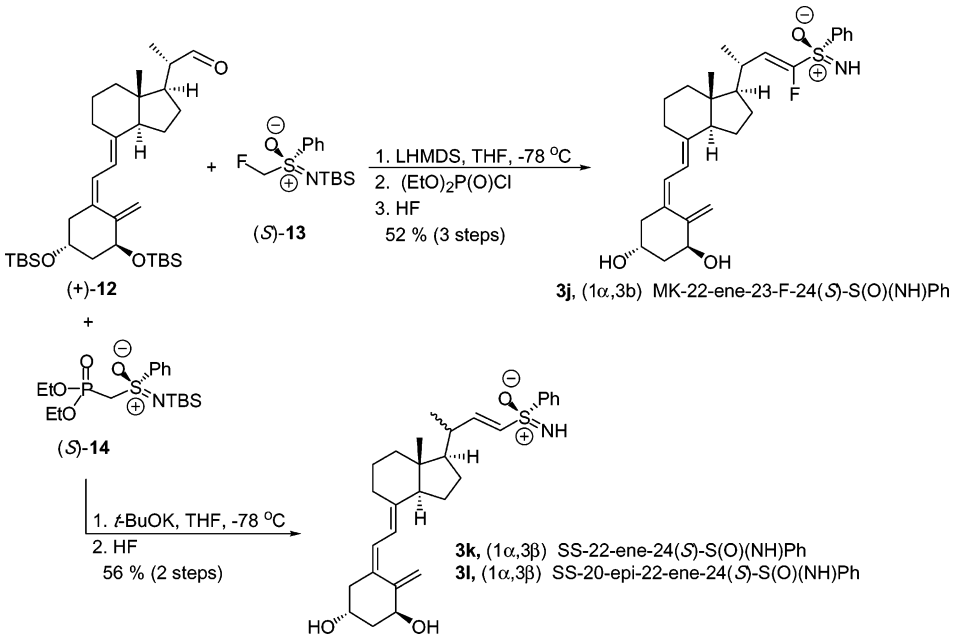
A standard biochemical assay[16] showed that, among the 24-NH sulfoximine analogues, 24-(*S*)-NH sulfoximine analogue **3a** is the strongest inhibitor of human CYP24 hydroxylase enzyme (Table 3). For comparison, analogue **3a** is a more potent CYP24 inhibitor than commonly used ketoconazole and other azole inhibitors.[17]

Our learning from the structure−activity relationships (SAR) among these sulfoximines includes the following: (1) The stereochemical configuration at the sulfur atom in each pair of diastereomeric sulfoximines is very important, with sulfoximines of the 24-(*S*) configuration having higher CYP24 inhibition potency than those with the 24-(*R*) configuration (CYP24 inhibitory activity: **3a** > **3b**, **3d** > **3c**, **3f** > **3g** and **3h** > **3i**). (2) Replacement of one of the oxygen atoms of sulfone analogue **2** by an NH group as in analogue **3a** increases the CYP24 inhibitory activity by about 4-fold. (3) The nature of the A-ring is of only minor importance, with CYP24 inhibitory activity being similar for the natural A-ring and for the 19-*nor* A-ring (e.g., **3a** vs **3d**), but the activity diminished when the 1α-hydroxy group was replaced by hydrogen atom (e.g., **3e** is 10 times less active than **3a**). (4) The electronic nature of the phenyl group is important, with CYP24 inhibitory activity decreasing as the terminal aromatic ring acquires lower electron density (CYP24 inhibitory activity R_2 = phenyl > 4-fluorophenyl). (5) The 22-ene version **3k** designed to slow side-chain catabolism is inactive. (6) The 22-

Scheme 3



Scheme 4



ene-23-fluoro sulfoximine analogue **3j** is also inactive. (7) The 20-*epi* analogue **3l** is much less active than parent sulfoximine **3a**.

We also analyzed whether sulfoximine **3a** had the ability to inhibit the enzyme activities of CYP27A and CYP27B, two cytochromes that are critical in the vitamin D biosynthesis pathway. Analogue **3a** had IC_{50} values of >1000 nM and 554 nM for inhibition of CYP27A1 and CYP27B, respectively. Thus, sulfoximine **3a** showed extraordinary selectivity for CYP24.

In summary, we have shown that NH sulfoximines, monoimino analogues of sulfones, are in general potent and selective inhibitors of the human cytochrome P450C24 (CYP24) hydroxylase enzyme. Specifically, 24-(*S*) sulfoximine **3a** is approximately 40 times more potent (IC_{50} = 7.4 nM) than the commonly used CYP24 inhibitor ketoconazole (IC_{50} = 312 nM). Analogue **3a** shows high inhibitory selectivity for CYP24 over the vitamin D-related cytochromes CYP27A and CYP27B. Thus, this new sulfoximine entity **3a**, having low-calcemic activity, has the potential to be used chemotherapeutically in conjunction with the natural hormone 1α,25-dihydroxyvitamin D_3 (**1**) to extend the hormone's lifetime and thus to require less of it for effective

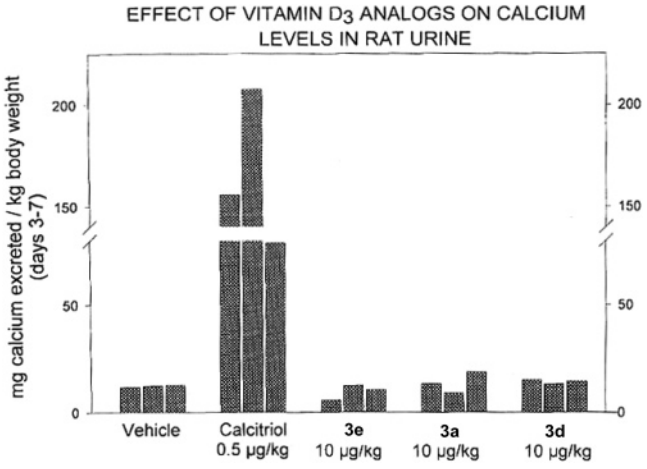


Figure 1. Effects of vitamin D_3 analogues on urinary calcium excretion in rats. Animals were treated with 0.5−10 μg/kg of body weight of test compound po for 7 consecutive days, and urinary excretion of calcium was measured during days 3−7. Values are mean ± SE from three animals in each group.

Table 3. CYP24 Inhibitory Activities of NH Sulfoximines

NH sulfoximine	CYP24 IC_{50}[a] (nM)
3a, MK-24(*S*)-S(O)(NH)Ph	7.4 ± 4.2
3b, MK-24(*R*)-S(O)(NH)Ph	28 ± 10
3c, MK-19-nor-24(*R*)-S(O)(NH)Ph	13 ± 11
3d, MK-19-nor-24(*S*)-S(O)(NH)Ph	9.7 ± 3.1
3e, MK-1-deoxy-24(*S*)-S(O)(NH)Ph	75 ± 40
3f, MK-23-cyclopropyl-24(*S*)-S(O)(NH)Ph	20.5 ± 3.5
3g, MK-23-cyclopropyl-24(*R*)-S(O)(NH)Ph	50 ± 38
3h, MK-24(*S*)-S(O)(NH)PFP	28 ± 20
3i, MK-24(*R*)-S(O)(NH)PFP	44 ± 48
3j, MK-22-ene-23-F-24(*S*)-S(O)(NH)Ph	>1000
3k, SS-22-ene-24(*S*)-S(O)(NH)Ph	>1000
3l, SS-20-epi-22-ene-24(*S*)-S(O)(NH)Ph	549 ± 45
ketoconazole	312 ± 1
2, KRC-24SO_2-Ph-1	28

[a] IC_{50} values represent the means and standard deviations from at least three independent experiments.

treatment of human diseases. Our progress in this effort will be reported in due course.

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 liquid reagents were transferred by syringe or cannula and were added into the flask through a rubber septum. Methylene chloride was freshly distilled from CaH_2 prior to use. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl immediately prior to use. All other solvents and reagents were used as received unless otherwise stated.

Both ^1H and ^{13}C spectra were obtained on a Varian XL 400 spectrometer at 400 and 100 MHz, respectively. All NMR spectra were obtained as a solution in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard unless otherwise stated. Infrared spectra were obtained on a Perkin-Elmer 1600 Fourier transform infrared (FT-IR) spectrometer as liquid films and thin layers with NaCl cells. 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 details for the specific compounds.

Flash chromatography was performed on 230−400 mesh silica gel (E. M. Science) with technical- and/or HPLC-grade solvents. Medium-pressure liquid chromatography (MPLC) was performed with an FMI pump and prepacked silica gel column (Merck, Labor Columns, LiChroprep Si 60, 40−63 mm). High-pressure liquid chromatography (HPLC) was performed on a Rainin HPLX system equipped with two 25 mL pump heads and a Rainin Dynamax UV-C dual-beam variable-wavelength detector set at 254 or 260 nm with Phenomenex, Luna 5 m C18 semipreparative (250 × 10 mm) column and Chiralcel OJ semipreparative (250 × 10 mm) column.

HRMS and LRMS were obtained on a Micromass QTOF electrospray mass spectroscopy with electronic or chemical ionization (EI or CI) at The Ohio State University.

(+)-(*S*)- and (−)-(*R*)-*S*-Methyl-*S*-phenylsulfoximine,[18] (±)-*S*-cyclopropyl-*S*-phenylsulfoximine,[19] compounds 22-iodide (+)-**4**,[20] N-silylated sulfoximines **5**,[10] A-ring phosphine oxides **8**,[14,21] iodide (+)-**9**,[11] and aldehyde (+)-**12**[12] were prepared as reported.

The purity of all target compounds was >97% by ^1H NMR and by analytical HPLC determination.

General Procedure for Preparation of Alcohols 6. A flame-dried 10-mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was charged with the appropriate *N-tert*-butyldimethylsilyl sulfoximine **5** (0.32 mmol) dissolved in 3.2 mL of freshly distilled tetrahydrofuran (THF) and 0.32 mL of hexamethylphosphoramide (HMPA). Then the flask was cooled to −78 °C in a 2-propanol/dry ice bath. To this solution was added *n*-BuLi (0.33 mmol, 0.23 mL, 0.44 M solution in hexanes) dropwise over several minutes, during which time a pale yellow color developed. This mixture was allowed to stir at −78 °C for an additional 30 min. Meanwhile, a flame-dried 10-mL pear-shaped flask equipped with a septum along with an Ar balloon was charged with iodide (+)-**4** (50 mg, 0.11 mmol) dissolved in 0.5 mL of freshly distilled THF and cooled to −78 °C in a 2-propanol/dry ice bath. The solution of iodide (+)-**4** was transferred into the flask containing the lithiated sulfoximine at −78 °C via cannula over several minutes. After the addition was complete, the mixture was gradually warmed to room temperature and stirred at this temperature for about 6 h. Thin-layer chromatography (TLC) showed the complete consumption of starting material. The reaction was quenched by addition of 2 mL of pH 7 buffer solution. Then it was rinsed into a separatory funnel with ethyl acetate. The mixture was extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with water (1 × 25 mL) and brine solution (1 × 25 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by flash column chromatography.

An argon-purged 5 mL polypropylene vial equipped with a magnetic stir bar was charged with appropriate alkylated C,D-ring bis-protected intermediate (0.065 mmol) and dissolved in 1.6 mL of acetonitrile to give ca. 0.04 M solution. To this well-stirred solution was added 0.26 of HF (6.5 mmol, 0.26 mL, 49% aqueous solution) via syringe at room temperature, and the mixture was then allowed to stir at room temperature for 4 h. TLC showed the completion of the reaction. This reaction mixture was diluted with ether (25 mL) and a saturated solution of $NaHCO_3$ was added until no more carbon dioxide was liberated. The reaction mixture was then rinsed into a separatory funnel with ethyl acetate and was extracted with ethyl acetate (4 × 25 mL). The combined extracts were washed with water (1 × 25 mL) and brine solution (1 × 25 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product.

C-8 Alcohol 6a. Flash column chromatography eluted with 100% ethyl acetate afforded 19.4 mg of (+)-**6a** as a viscous oil in 86% yield. Data for (+)-**6a**: $[\alpha]_D^{25} = +30.2$ (*c* 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.95 (m, 2H), 7.64−7.53 (m, 3H), 4.05 (br s, 1H), 3.20 (ddd, 1H, J = 4.4, 12.0, and 13.6 Hz), 3.03 (ddd, 1H, J = 4.4, 12.0, and 13.6 Hz), 2.67 (br s, 1H), 1.93−1.68 (m, 6H), 1.58−1.37 (m, 5H), 1.30−0.95 (m, 5H), 0.87 (s, 3H), 0.84 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.9, 132.9, 129.1, 128.3, 69.0, 55.8, 54.8, 52.4, 41.8, 40.2, 34.1, 33.5, 28.5, 26.8, 22.3, 18.2, 17.3, 13.4; IR (thin film) 3436 (br, w), 3330 (br, w), 2934 (s), 2871 (s), 1445 (m), 1373 (w), 1219 (br, s), 1161 (w), 1097 (sh, m), 989 (s, m), 753 (s) cm^{-1}; HRMS calcd for $C_{20}H_{31}NO_2SNa^+$ [M + Na] 372.1967, found 372.1968.

C-8 Alcohol 6b. Flash column chromatography eluted with 100% ethyl acetate afforded 20.1 mg of (+)-**6b** as a viscous oil in 89% yield. Data for (+)-**6b**: $[\alpha]_D^{25} = +23.7$ (*c* 1.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99−7.96 (m, 2H), 7.66−7.54 (m, 3H), 4.07 (br s, 1H), 3.19 (ddd, 1H, J = 4.8, 12.4, and 13.6 Hz), 3.07 (ddd, 1H, J = 4.4, 11.6, and 13.6 Hz), 2.68 (br s, 1H), 1.95−1.78 (m, 4H), 1.75−1.62 (m, 2H), 1.58−1.36 (m, 5H),1.32−0.95 (m, 5H), 0.89 (s, 3H), 0.87 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.9, 132.9, 129.1, 128.3, 69.0, 55.7, 54.7, 52.4, 42.8, 40.2, 34.1, 33.5, 28.5, 26.8, 22.3, 18.2, 17.3, 13.4; IR (thin film) 3448 (br, w), 3330 (br, w), 2935 (s), 2871 (s), 1445 (m), 1219 (br, s), 1098 (sh, m), 1078 (br, s), 990 (s), m), 753 (s) cm^{-1}; HRMS calcd for $C_{20}H_{31}NO_2SNa^+$ [M + Na] 372.1967, found 372.1981.

C-8 Alcohol 6c. Flash column chromatography eluted with 50% ethyl acetate afforded 50 mg of **6c** as a viscous oil in 73% overall yield. Data for **6c** (as a mixture of diastereomers): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.95 (m, 4H), 7.63−7.58 (m, 2H), 7.55−7.50 (m, 4H), 4.03 (br s, 2H), 2.14 (t, 4H, J = 11.2 Hz), 1.90 (d, 2H, J = 13.2 Hz), 1.78−1.20 (m, 22H), 1.08−0.88 (m, 12H), 0.86 (s, 3H), 0.83 (s, 3H), 0.78−0.70 (m, 2H), 0.71 (d, 3H, J = 6.4 Hz), 0.68 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.2, 140.50, 132.77, 132.70, 128.97, 128.88, 128.74, 69.05, 57.06, 56.97, 52.40, 41.93, 40.26, 40.20, 37.56, 37.13, 33.46, 33.26, 27.18, 27.13, 22.38, 18.78, 17.28, 13.48, 12.41, 12.27, 12.20, 11.67; IR (thin film) 3448 (br, w), 3330 (br, m), 3271 (m), 2931 (s), 2860 (s), 1443 (m), 1219 (br, s), 1067 (sh, m), 984 (s), 967 (m), 755 (s) cm^{-1}; HRMS calcd for $C_{22}H_{33}NO_2SNa^+$ [M + Na] 398.2124, found 398.2121.

General Procedure for Preparation of Ketones 7. A flame-dried 10-mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was charged with the appropriate alcohol **6** (0.043 mmol) dissolved in 1 mL of freshly distilled CH_2Cl_2 to give ca. 0.04 M solution. To this solution were added PDC (34 mg, 0.09 mmol) and 21 mg of oven-dried Celite in one portion at room temperature. The resulting mixture was allowed to stir at room temperature for about 12 h. TLC showed the complete consumption of starting material. The mixture was directly purified by column chromatography.

Ketone 7a. Flash column chromatography eluted with 100% ethyl acetate afforded 12 mg of ketone (+)-**7a** in 81% yield. Data for (+)-**7a**: $[\alpha]_D^{25} = +9.2$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.95 (m, 2H), 7.65−7.54 (m, 3H), 3.21 (ddd, 1H, J = 4.4, 12.0, and 13.6 Hz), 3.04 (ddd, 1H, J = 4.4, 12.0, and 13.6 Hz), 2.67 (s, 1H), 2.42 (dd, 1H, J = 8.0 and 11.6 Hz), 2.30−2.16 (m, 2H), 2.05−1.95 (m, 2H), 1.93−1.65 (m, 5H), 1.60−1.35 (m, 4H), 1.27−1.19 (m, 1H), 0.91 (d, 3H, J = 6.4 Hz), 0.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.6, 141.9, 133.0, 129.2, 128.3, 61.7, 55.9, 54.7, 49.7, 40.8, 38.8, 34.4, 28.6, 27.2, 23.9, 18.9, 18.4, 12.4; IR (thin film) 3271 (w), 2942 (s), 2872 (s), 1701 (s), 1437 (sh, m), 1378 (w), 1219 (br, s), 1102 (w), 978 (m), 755(w) cm^{-1}; HRMS calcd for $C_{20}H_{29}NO_2SNa^+$ [M + Na] 370.1811, found 370.1793.

Ketone 7b. Flash column chromatography eluted with 100% ethyl acetate afforded 13 mg of ketone (+)-**7b** in 87% yield. Data for (+)-**7b**: $[\alpha]_D^{25} = +8.0$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.95 (m, 2H), 7.65−7.54 (m, 3H), 3.18 (ddd, 1H, J = 4.8, 12.0, and 13.6 Hz), 3.08 (ddd, 1H, J = 4.8, 12.0, and 13.6 Hz), 2.67 (s, 1H), 2.41 (dd, 1H, J = 7.6 and 10.8 Hz), 2.30−2.16 (m, 2H), 2.06−1.95 (m, 2H), 1.93−1.80 (m, 2H), 1.78−1.64 (m, 3H), 1.57−1.33 (m, 4H), 1.27−1.19 (m, 1H), 0.92 (d, 3H, J = 6.8 Hz), 0.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.6, 141.9, 133.0, 129.1, 128.3, 61.7, 55.8, 54.6, 49.7, 40.8, 38.8, 34.4, 28.6, 27.1, 23.9, 18.9, 18.4, 12.4; IR (thin film) 3271 (w), 2954 (s), 2872 (s), 1701 (s), 1443 (sh, m), 1219 (br, s), 1096 (s), 978 (m), 749 (w) cm^{-1}; HRMS calcd for $C_{20}H_{29}NO_2SNa^+$ [M + Na] 370.1811, found 370.1809.

Ketone 7c. Flash column chromatography eluted with 50% ethyl acetate afforded 42 mg of ketone **7c** as an approximately 1:1 mixture of diastereomers in 85% yield. Data for **7c** (as a mixture): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99−7.94 (m, 4H), 7.65−7.60 (m, 2H), 7.57−7.54 (m, 4H), 2.8 (br s, 2H), 2.39−2.34 (m, 2H), 2.29−2.14 (m, 4H), 2.04−1.94 (m, 4H), 1.92−1.58 (m, 10H), 1.54−1.35 (m, 6H), 1.28−1.20 (m, 2H), 1.12−0.91 (m, 6H), 0.81 (d, 3H, J = 6.4 Hz), 0.77 (d, 3H, J = 6.4 Hz), 0.79−0.69 (m, 4H), 0.58 (s, 3H), 0.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.65, 139.98, 133.10, 133.02, 129.02, 128.92, 61.75, 57.09, 57.00, 49.85, 40.15, 38.81, 38.78, 37.82, 37.36, 33.62, 27.49, 27.43, 23.89, 19.00, 18.94, 12.71, 12.52, 12.49, 12.44, 11.83; IR (thin film) 3278 (m), 2957 (s), 2874 (m), 1708 (s), 1445 (sh, m), 1378 (w), 1220 (br, s), 1109 (w), 968 (m), 749 (m) cm^{-1}; HRMS calcd for $C_{22}H_{31}NO_2SNa^+$ [M + Na] 396.1967, found 396.1955.

General Procedure for Preparation of Sulfoximine Analogues 3 and 3′. The corresponding A-ring phosphine oxide **8** and C,D-ring ketone **7** were azeotropically dried with anhydrous benzene (4 × 4 mL) on a rotary evaporator and held under vacuum (ca. 0.1 mmHg) for at least 48 h prior to use.

A flame-dried 10-mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was charged with phosphine oxide **8** (0.11 mmol) dissolved in 1.1 mL of freshly distilled THF to give ca. 0.1 M solution. Then the flask was cooled to −78 °C in a 2-propanol/dry ice bath. To this solution was added *n*-BuLi (68 μL, 0.11 mmol, 1.6 M solution in hexanes) dropwise over several minutes, during which time a deep red color developed and persisted. This mixture was allowed to stir at −78 °C for an additional 10 min. Meanwhile, a flame-dried 10-mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was previously charged with CD-ring ketone **7** (12 mg, 0.036 mmol) dissolved in 1 mL of freshly distilled THF and cooled to −78 °C in a 2-propanol/dry ice bath. The solution of CD-ring ketone was transferred dropwise into the flask containing the phosphine oxide anion at −78 °C via cannula over several minutes. After the addition was complete, the deep red color persisted and the mixture was allowed to stir at −78 °C for ca. 15 h, during which time it was visually checked. Upon observation of the light yellow color, the reaction was quenched at −78 °C by addition of 5 mL of pH 7 buffer and allowed to come to room temperature. The mixture was then rinsed into a separatory funnel with ethyl acetate and extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with water (1 × 25 mL) and brine solution (1 × 25 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product, which was purified by column chromatography eluted with 50% ethyl acetate in hexanes in the presence of 1% triethylamine, affording the coupled product.

This coupled product (0.018 mmol) was charged into a 5 mL argon-purged polypropylene vial equipped with a magnetic stir bar and dissolved in 0.9 mL of acetonitrile to give ca. 0.02 M solution. To this well-stirred solution was added HF (1.8 mmol, 75 mL, 49% aqueous solution) via syringe at room temperature, and the mixture was then allowed to stir at room temperature in the dark for 2 h. TLC showed the completion of the reaction. This reaction mixture was diluted with ether (25 mL), and a saturated solution of $NaHCO_3$ was added until no more carbon dioxide was liberated. The reaction mixture was then rinsed into a separatory funnel with ethyl acetate and was extracted with ethyl acetate (5 × 25 mL). The combined extracts were washed with water (1 × 25 mL) and brine solution (1 × 25 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography.

Sulfoximine Analogues 3a and 3′a. Flash column chromatography eluted with 99% ethyl acetate in the presence of 1% triethylamine to afford 8.4 mg of a mixture of diastereomers (+)-**3a** and (+)-**3′a** in 92% yield and in a ratio of 2.5:1, respectively. This diastereomeric mixture was then separated by HPLC on a Chiralcel OJ column [semipreparative (1 × 25 cm), flow rate = 2.0 mL/min] eluted with 13% ethanol in hexanes to afford 1.9 mg of (+)-**3a** and 1.0 mg of (+)-**3′a** in 21% and 11% yields, respectively. The retention time for (+)-**3a** is 58.1 min, and for (+)-**3′a**, 45.7 min. Data for (+)-**3a**: $[\alpha]_D^{25} = +80.4$ (*c* 0.13, MeOH); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.96 (m, 2H), 7.64−7.52 (m, 3H), 6.36 (d, 1H, J = 11.2 Hz), 5.99 (d, 1H, J = 11.2 Hz), 5.32 (t, 1H, J = 1.6 Hz) 4.98

(br s, 1H), 4.43−4.40 (m, 1H), 4.23−4.22 (m, 1H), 3.20 (ddd, 1H, J = 4.4, 12.4, and 13.2 Hz), 3.03 (ddd, 1H, J = 4.8, 12.4, and 13.2 Hz), 2.82−2.78 (m, 1H), 2.65 (s, 1H), 2.61−2.58 (m, 1H), 2.33−2.28 (m, 1H) 2.04−1.90 (m, 3H), 1.82−1.75 (m, 2H), 1.69−1.42 (m, 8H), H), 1.28−1.20 (m, 4H), 0.88 (d, 3H, J = 6.4 Hz), 0.49 (s, 3H); ^{13}C NMR (CH_3OD-d_3, 100 MHz) δ 149.9, 142.3, 140.8, 136.0, 135.2, 130.7, 129.9, 124.9, 119.3, 112.2, 71.6, 67.5, 57.5, 57.2, 55.5, 47.0, 46.2, 43.8, 41.8, 36.4, 30.3, 30.0, 28.4, 24.7, 23.3, 19.1, 12.4; IR 3387 (br, m), 3307 (br, m), 2942 (s), 2872 (m), 1443 (m), 1349 (w), 1213 (s), 1096 (m), 1055 (s), 1008 (m), 984 (sh, s), 749 (s) cm^{-1}; HRMS calcd for $C_{29}H_{41}NO_3SNa^+$ [M + Na] 506.2699, found 506.2668; UV (MeOH) λ_{max} 265 nm (ϵ 16 640). Data for (+)-**3′a**: $[\alpha]_D^{25}$ = +9 (c 0.09, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.96 (m, 2H), 7.64−7.52 (m, 3H), 6.37 (d, 1H, J = 11.6 Hz), 5.98 (d, 1H, J = 11.6 Hz), 5.31 (m, 1H) 4.98 (br s, 1H), 4.43−4.41 (m, 1H), 4.23−4.19 (m, 1H), 3.23−317 (m, 1H), 3.07−2.99 (m, 1H), 2.83−2.80 (m, 1H), 2.66 (s, 1H), 2.62−2.60 (m, 1H), 2.32−2.27 (m, 1H) 2.00−1.90 (m, 5H), 1.81−1.64 (m, 7H), 1.25−1.21 (m, 6H), 0.87 (d, 3H, J = 6.8 Hz), 0.48 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 149.8, 142.4, 142.2, 135.9, 130.5, 129.8, 124.9, 124.9, 119.2, 112.4, 71.7, 67.5, 57.2, 55.8, 47.0, 46.4, 43.8, 41.8, 36.4, 30.5, 30.0, 28.4, 24.7, 23.4, 19.1, 12.4; IR: 3320 (br, m), 3307, 2940 (s), 2871 (m), 1445 (m), 1349 (w), 1214 (s), 1093 (m), 1053 (s), 1008 (m), 984 (sh, s), 749 (s) cm^{-1}; HRMS calcd for $C_{29}H_{41}NO_3SNa^+$ [M + Na] 506.2699, found 506.2690.

Sulfoximine Analogues 3b and 3′b. Flash column chromatography eluted with 99% ethyl acetate in the presence of 1% triethylamine afforded 7.2 mg of a mixture of diastereomers (+)-**3b** and (−)-**3′b** in 82% yield and in a ratio of 2.9:1, respectively. This diastereomeric mixture was then separated by HPLC on a Chiralcel OJ column [semipreparative (1 × 25 cm), flow rate = 2.0 mL/min] eluted with 13% ethanol in hexanes to afford 2.2 mg of (+)-**3b** and 1.0 mg of (+)-**3′b** in 25% and 11% yields, respectively. The retention time for (+)-**3b** is 49.2 min, and for (+)-**3′b**, 40.2 min. Data for (+)-**3b**: $[\alpha]_D^{25}$ = +37.3 (c 0.13, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.95 (m, 2H), 7.65−7.52 (m, 3H), 6.36 (d, 1H, J = 11.6 Hz), 5.99 (d, 1H, J = 11.2 Hz), 5.31 (m, 1H) 4.98 (br s, 1H), 4.43−4.40 (m, 1H), 4.29−4.22 (m, 1H), 3.18 (ddd, 1H, J = 4.8, 12.4, and 14.0 Hz), 3.07 (ddd, 1H, J = 4.8, 12.4, and 14.0 Hz), 2.83−2.80 (m, 1H), 2.66 (s, 1H), 2.61−2.58 (m, 1H), 2.33−2.28 (m, 1H) 2.20−1.80 (m, 6H), 1.74−1.62 (m, 8H), 1.30−1.116 (m, 4H), 0.88 (d, 3H, J = 6.4 Hz), 0.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6, 142.5, 133.2, 129.6, 128.6, 128.2, 124.8, 117.3, 111.8, 70.8, 66.8, 56.1, 55.7, 54.1, 45.9, 45.2, 42.8, 40.3, 34.9, 28.9, 28.2, 27.2, 23.4, 22.1, 18.5, 11.9; IR 3377 (br, m), 3318 (br, m), 2931 (s), 2872 (m), 1442 (m), 1214 (s), 1096 (m), 1055 (s), 1008 (m), 984 (sh, s), 749 (s) cm^{-1}; HRMS calcd for $C_{29}H_{41}NO_3SNa^+$ [M + Na] 506.2699, found 506.2676; UV (MeOH) λ_{max} 265 nm (ϵ 15 383). Data for (+)-**3′b**: $[\alpha]_D^{25}$ = +17.5 (c 0.09, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.95 (m, 2H), 7.64−7.52 (m, 3H), 6.37 (d, 1H, J = 11.2 Hz), 5.98 (d, 1H, J = 11.2 Hz), 5.31 (m, 1H), 4.98 (br s, 1H), 4.43−4.41 (m, 1H), 4.22−4.19 (m, 1H), 3.16 (ddd, 1H, J = 4.4, 12.0, and 13.2 Hz), 3.08 (ddd, 1H, J = 4.4, 12.4, and 13.2 Hz), 2.82−2.80 (m, 1H), 2.66 (s, 1H), 2.62−2.58 (m, 1H), 2.31−2.27 (m, 1H) 1.91−1.80 (m, 4H), 1.74−1.60 (m, 10H), 1.30−1.19 (m, 4H), 0.88 (d, 3H, J = 6.4 Hz), 0.50 (s, 3H); due to insufficient amount, ^{13}C NMR was not obtained; IR 3307 (br, m), 2919 (s), 2860 (m), 1443 (m), 1219 (s), 1090 (m), 1055 (s), 984 (sh, s), 749 (s) cm^{-1}; HRMS calcd for $C_{29}H_{41}NO_3SNa^+$ [M + Na] 506.2699, found 506.2673.

Sulfoximine Analogue 3c. Flash column chromatography eluted with 99% ethyl acetate in the presence of 1% triethylamine afforded 9.1 mg of (+)-**3c** in 91% yield. This analogue was then further purified by HPLC on a Chiralcel OJ column [semipreparative (1 × 25 cm), flow rate = 2.5 mL/min] eluted with 15% ethanol in hexanes to afford 7 mg (+)-**3c** in 70% yield. The retention time for (+)-**3c** is 30.25 min. Data for (+)-**3c**: $[\alpha]_D^{25}$ = +101.6 (c 0.46, MeOH); ^{1}H NMR (MeOD-d_3, 400 MHz) δ 7.98−7.96 (m, 2H), 7.73−7.62 (m, 3H), 6.20 (d, 1H, J = 11.2 Hz), 5.86 (d, 1H, J = 11.2 Hz), 4.04−3.96 (m, 2H), 3.26 (dd, 1H, J = 4.8 and 12.0 Hz), 3.15 (ddd, 1H, J = 4.8, 11.6, and 14.0 Hz), 2.81 (dd, 1H, J = 3.6 and 12.4 Hz), 2.58 (dd, 1H, J = 3.6 and 13.6 Hz), 2.40 (dd, 1H, J = 2.8 and 13.6 Hz), 2.23−2.13 (m, 2H), 2.02−1.94 (m, 2H), 1.87−1.45 (m, 11H), 1.39−1.14 (m, 5H), 0.90 (d, 3H, J = 6.8 Hz), 0.52 (s, 3H); ^{13}C NMR (MeOD-d_3, 100 MHz) δ 142.11, 141.90, 134.66, 134.19, 130.55, 129.81, 123.50, 117.41, 68.11, 67.83, 57.45, 57.24, 55.70, 46.88, 45.55, 42.80, 41.81, 37.76, 36.41, 30.47, 29.88, 28.44, 24.57, 23.31, 19.12, 12.48; IR 3330 (m, br), 2942 (s), 2872 (s), 1437 (m), 1213 (br, s), 1096 (m), 1049 (m), 978 (m), 749 (s) cm^{-1}; HRMS calcd for $C_{28}H_{41}NO_3SNa^+$ [M + Na] 494.2699, found 494.2707; UV (MeOH) λ_{max} 251 nm (ϵ 28 100).

Sulfoximine Analogue 3d. Flash column chromatography eluted with 99% ethyl acetate in the presence of 1% triethylamine afforded 3.7 mg of (+)-**3d** in 70% yield. This analogue was then further purified by HPLC on a Chiralcel OJ column [semipreparative (1 × 25 cm), flow rate = 2.5 mL/min] eluted with 15% ethanol in hexanes to afford 2.3 mg of (+)-**3d** in 43% yield. The retention time for (+)-**3d** is 35.22 min. Data for (+)-**3d**: $[\alpha]_D^{25}$ = +82.3 (c 0.16, MeOH); ^{1}H NMR (MeOD-d_3, 400 MHz) δ 7.98−7.96 (m, 2H), 7.73−7.61 (m, 3H), 6.20 (d, 1H, J = 11.2 Hz), 5.86 (d, 1H, J = 11.2 Hz), 4.05−3.96 (m, 2H), 3.26 (dd, 1H, J = 4.0 and 11.6 Hz), 3.19−3.13 (m, 1H), 2.81 (dd, 1H, J = 3.6 and 11.6 Hz), 2.58 (dd, 1H, J = 4.0 and 13.6 Hz), 2.40 (dd, 1H, J = 3.6 and 14.0 Hz), 2.23−2.13 (m, 2H), 2.03−1.93 (m, 2H), 1.84−1.46 (m, 12H), 1.33−1.17 (m, 5H), 0.89 (d, 3H, J = 6.0 Hz), 0.51 (s, 3H); ^{13}C NMR (MeOD-d_3, 100 MHz) δ 142.17, 141.91, 134.66, 134.20, 130.55, 129.81, 123.51, 117.41, 68.11, 67.84, 57.46, 57.29, 55.81, 46.89, 45.55, 42.81, 41.83, 37.76, 36.43, 30.52, 29.88, 28.46, 24.57, 23.31, 19.10, 12.49; IR 3330 (m, br), 2942 (s), 2872 (s), 1443 (m), 1213 (br, s), 1096 (m), 1049 (m), 978 (s), 755 (s) cm^{-1}; HRMS calcd for $C_{28}H_{41}NO_3SNa^+$ [M + Na] 494.2699, found 494.2679; UV (MeOH) λ_{max} 251 nm (ϵ 32 661).

Sulfoximine Analogue 3e. Flash column chromatography eluted with 99% ethyl acetate in the presence of 1% triethylamine afforded 10.6 mg of (+)-**3e** in 88% yield. This analogue was then further purified by HPLC on a Chiralcel OJ column [semipreparative (1 × 25 cm), flow rate = 2.5 mL/min] eluted with 10% ethanol in hexanes to afford 3.0 mg of (+)-**3e** in 28% yield. The retention time for (+)-**3e** is 31.47 min. Data for (+)-**3e**: $[\alpha]_D^{25}$ = +36.6 (c 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.96 (m, 2H), 7.64−7.53 (m, 3H), 6.21 (d, 1H, J = 11.6 Hz), 6.00 (d, 1H, J = 11.2 Hz), 5.05−5.04 (m, 1H), 4.80 (d, 1H, J = 2.4 Hz), 3.96−3.91 (m, 1H), 3.20 (ddd, 1H, J = 4.4, 12.4, and 13.6 Hz), 3.04 (ddd, 1H, J = 4.4, 11.2, and 13.6 Hz), 2.80 (dd, 1H, J = 4.4 and 12.4 Hz), 2.56 (dd, 1H, J = 4.0 and 13.2 Hz), 2.43−2.36 (m, 1H), 2.33 (dd, 1H, J = 7.6 and 13.2 Hz) 2.20−2.13 (m, 1H), 1.96−190 (m, 4H), 1.82−1.42 (m, 10H), 1.28−1.16 (m, 4H), 0.87 (d, 3H, J = 6.4 Hz), 0.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 142.0, 141.6, 135.3, 132.9, 129.1, 128.3, 122.2, 117.7, 112.4, 69.2, 56.1, 55.7, 54.8, 45.9, 45.7, 40.3, 35.2, 35.0, 31.9, 28.8, 28.7, 27.3, 23.4, 22.1, 18.5, 11.9; IR 3295 (m, br), 2931 (s), 2860 (m), 1443 (m), 1213 (br, s), 1096 (m), 1061 (w), 984 (m), 749 (s) cm^{-1}; HRMS calcd for $C_{29}H_{41}NO_2SNa^+$ [M + Na] 490.2750, found 490.2723; UV (MeOH) λ_{max} 265 nm (ϵ 15 648).

Sulfoximine Analogues 3f and 3g. Flash column chromatography eluted with 99% ethyl acetate in the presence of 1% triethylamine afforded 8.2 mg of a mixture of diastereomers (+)-**3f** and (+)-**3g** in 79% overall yield and in a ratio of approximately 1:1. This diastereomeric mixture was then separated by HPLC on a Chiralcel OJ column [semipreparative (1 × 25 cm), flow rate = 2.0 mL/min] eluted with 7% ethanol in hexanes to afford 1.2 mg of (+)-**3g** and 1.9 mg of (+)-**3f** in 30% and 48% yields, respectively. The retention time for (+)-**3g** is 123.3 min, and for (+)-**3f**, 137.5 min. Data for (+)-**3f**: $[\alpha]_D^{25}$ = +37.7 (c 0.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.95 (m, 2H), 7.63−7.59 (m, 1H), 7.56−7.52 (m, 2H), 6.36 (d, 1H, J = 11.2 Hz), 5.99 (d, 1H, J = 11.2 Hz), 5.33 (m, 1H) 4.99−4.98 (br s, m, 1H), 4.45−4.41 (m, 1H), 4.26−4.17 (m, 1H), 2.79 (dd, 1H, J = 4.0 and 12.4 Hz), 2.59 (dd, 1H, J = 3.6 and 13.6 Hz), 2.54 (s, 1H), 2.31 (dd, 1H, J = 6.4 and 13.6 Hz), 2.13 (d, 1H, J = 14.8 Hz), 2.05−1.99 (m, 1H), 1.95−1.88 (m, 4H), 1.77−1.59 (m, 5H), 1.48−1.20 (m, 7H), 1.11−0.86 (m, 2H), 0.73

(d, 3H, $J = 6.4$ Hz), 0.76−0.70 (m, 2H), 0.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.59, 142.70, 140.75, 133.08, 129.47, 128.78, 128.55, 124.84, 117.18, 111.79, 70.80, 66.81, 56.94, 56.18, 45.92, 45.22, 42.85, 40.32, 40.29, 37.40, 34.13, 28.95, 27.66, 23.44, 22.22, 19.11, 12.41,12.03,11.74; IR 3334 (br, m), 2936 (s), 2872 (m), 1445 (m), 1284 (s), 1215 (br, m), 1119 (m), 1053 (br, s), 978 (w) 753 (s) cm^{-1}; HRMS calcd for $C_{31}H_{43}NO_3SNa^+$ [M + Na] 532.2855, found 532.2860; UV (MeOH) λ_{max} 265 nm (ϵ 15 684). Data for (+)-**3g**: $[\alpha]_D^{25} = +8.5$ (c 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.94 (m, 2H), 7.62−7.58 (m, 1H), 7.55−7.51 (m, 2H), 6.36 (d, 1H, $J = 11.6$ Hz), 5.98 (d, 1H, $J = 11.2$ Hz), 5.33 (m, 1H), 4.99 (br s, 1H), 4.45−4.41 (m, 1H), 4.26−4.20 (m, 1H), 2.80 (dd, 1H, $J = 4.4$ and 12.8 Hz), 2.59 (dd, 1H, $J = 3.6$ and 13.6 Hz), 2.50 (s, 1H), 2.31 (dd, 1H, $J = 6.8$ and 13.6 Hz), 2.15 (d, 1H, $J = 14.4$ Hz), 2.05−1.99 (m, 1H), 1.95−1.88 (m, 4H), 1.77−1.59 (m, 5H), 1.48−1.20 (m, 7H), 1.11−0.86 (m, 2H), 0.75 (d, 3H, $J = 6.0$ Hz), 0.75−0.72 (m, 2H), 0.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.62, 142.74, 141.50, 133.06, 129.38, 128.77, 128.46, 124.87, 117.17, 111.76, 70.82, 66.84, 57.05, 56.19, 54.1, 45.93, 45.24, 42.88, 40.33, 37.80, 34.11, 28.96, 27.61, 23.45, 22.21, 19.13, 12.29 (2C), 12.01; IR 3330 (br, m), 2931 (s), 2872 (m), 1443 (m), 1219 (s), 1072 (m), 961 (sh, s), 890 (w) 749 (s) cm^{-1}; HRMS calcd for $C_{31}H_{43}NO_3SNa^+$ [M + Na] 532.2855, found 532.2826; UV (MeOH) λ_{max} 265 nm (ϵ 9024).

Preparation of *p*-Fluorophenylmethyl Sulfoximine 10. A flame-dried 25-mL recovery flask equipped with a magnetic stir bar, a septum, and an addition funnel along with an Ar balloon was charged with *p*-fluorophenylmethyl sulfide (1 g, 7 mmol) dissolved in 14 mL of freshly distilled CH_2Cl_2. Then the flask was cooled to 0 °C in an ice bath. To this solution was added mCPBA (1.9 g 7.7 mmol, 70%) as a solution in 5 mL of CH_2Cl_2 dropwise via addition funnel over several minutes. This mixture was allowed to stir at 0 °C for an additional 2 h. TLC showed complete consumption of the starting material. The reaction was quenched by addition of water and then rinsed into a separatory funnel with 50 mL of CH_2Cl_2. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined extracts were washed with saturated $NaHCO_3$ solution (1 × 10 mL) and brine solution (1 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by flash column chromatography eluted with 100% ethyl acetate. affording 1 g of sulfoxide as an oil in 90% yield.

This sulfoxide (1 g, 6.3 mmol) was charged into a flame-dried 25-mL recovery flask equipped with a magnetic stir bar, a septum, and an addition funnel along with an Ar balloon and dissolved in 6.3 mL of $CHCl_3$. Then, 0.45 g of NaN_3 (6.9 mmol) was added into the flask neat. Meanwhile, 1.53 mL of concentrated H_2SO_4 was charged into the addition funnel and allowed to drip into the reaction flask at 0 °C over several minutes. The addition funnel was then replaced with a reflux condenser and the flask was placed into an oil bath and heated to 45 °C for overnight. TLC showed complete consumption of the starting material. The reaction flask was cooled to room temperature and the reaction was quenched by addition of water, then the product rinsed into a separatory funnel with 50 mL of $CHCl_3$. The mixture was extracted with $CHCl_3$ (3 × 25 mL). The combined extracts were washed with brine solution (1 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by flash column chromatography eluted with 100% ethyl acetate affording 0.81 g of sulfoximine as a solid in 74% yield. This was recrystallized from ethyl acetate: mp 93−94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06−8.02 (m, 2H), 7.26−7.21 (m, 2H), 3.12 (s, 3H), 2.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.37 (d, $J = 253.7$ Hz), 139.4 (d, $J = 2.7$ Hz), 130.5 (d, $J = 9.1$ Hz), 116.3 (d, $J = 22.8$ Hz), 46.3; ^{19}F NMR ($CDCl_3$, 375 MHz) δ −105.6; IR 3268 (m), 3102 (w), 2928 (w), 1589 (s), 1493 (s), 1404 (w), 1321 (w), 1224 (s), 1094 (s), 1021 (m), 1004 (s), 946 (m), 840 (m), 817 (m), 753 (m) cm^{-1}; HRMS calcd for $C_7H_8FNOSNa^+$ [M + Na] 196.0202, found 196.0201.

A flame-dried 5-mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was charged with *p*-fluorophenylmethyl sulfoximine (0.1 g, 0.58 mmol) dissolved in 1.1 mL of anhydrous pyridine to give ca. 0.5 M solution. To this solution was added TBSCl (0.1 g, 0.69 mmol) neat in one portion. This mixture was allowed to stir at room temperature for 12 h. TLC showed complete consumption of the starting material. The reaction was quenched by addition of water and then rinsed into a separatory funnel with 25 mL of ethyl acetate. The mixture was extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with brine solution (1 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by flash column chromatography eluted with 10% ethyl acetate, affording 0.15 g of sulfoximine (±)-**10** as an oil in 90% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.93 (m, 2H), 7.20−7.14 (m, 2H), 2.99 (s, 3H), 0.91 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.9 (d, $J =$ 252.9 Hz), 141.2 (d, $J = 3.0$ Hz), 129.6 (d, $J = 8.1$ Hz), 116.0 (d, $J = 22.0$ Hz), 49.7, 25.9, 17.9, −2.57; ^{19}F NMR ($CDCl_3$, 375 MHz) δ −107.3; IR 2954 (s), 2958 (s), 2885 (s), 2855 (s), 1589 (m), 1493 (m), 1322 (s), 1302 (s), 1284 (s), 1250 (m), 1163 (s), 1150 (s), 1090 (w), 1006 (w), 953 (w), 834 (s), 814 (m), 774 (s) cm^{-1}; HRMS calcd for $C_{13}H_{22}FNOSSiNa^+$ [M + Na] 310.1067, found 310.1043.

Sulfoximine Analogues 3h and 3i. A flame-dried 5 mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was charged with (±)-**10** (8.4 mg, 0.029 mmol) dissolved in 0.5 mL of freshly distilled THF. Then the flask was cooled to −78 °C in a 2-propanol/dry ice bath. To this solution was added 19 mL of *n*-BuLi (0.03 mmol, 1.6 M solution in hexanes) dropwise over several minutes, followed by addition of 50 mL of HMPA, resulting in a yellow color. This mixture was allowed to stir at −78 °C for an additional 30 min. Meanwhile, a flame-dried 5 mL pear-shaped flask equipped with a septum along with an Ar balloon was charged with iodide (+)-**9** (5 mg, 0.0073 mmol), dissolved in 0.5 mL of freshly distilled THF and cooled to −78 °C in a 2-propanol/dry ice bath. The solution of iodide (+)-**9** was transferred into the flask containing the lithiated sulfoximine at −78 °C via cannula over a few minutes. After the addition was complete, the mixture was stirred at −78 °C for about 4−5 h. TLC showed almost complete consumption of (+)-**9**. The reaction was quenched by addition of 1 mL of pH 7 buffer and then rinsed into a separatory funnel with ethyl acetate. The mixture was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with water (1 × 10 mL) and brine solution (1 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by flash column chromatography eluted first with 100 mL of 100% hexanes and then with 10% ethyl acetate in hexanes, affording 3.4 mg of **11** in 55% yield.

An argon-purged 5 mL polypropylene vial equipped with a magnetic stir bar along with a cap was charged with **11** (3.4 mg, 0.004 mmol) dissolved in 0.4 mL of acetonitrile to give ca. 0.01 M solution. To this well-stirred solution was added HF (0.44 mmol, 16 μL, 49% aqueous solution) via syringe at room temperature, and the mixture was then allowed to stir at room temperature in the dark for 4 h. TLC showed the completion of the reaction. This reaction mixture was diluted with ether (10 mL), and a saturated solution of $NaHCO_3$ was added until no more carbon dioxide was liberated. The reaction mixture was then rinsed into a separatory funnel with ethyl acetate and extracted with ethyl acetate (4 × 10 mL). The combined extracts were washed with water (1 × 10 mL) and brine solution (1 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product, which was purified by flash column chromatography eluted with 99% ethyl acetate in the presence of 1% triethylamine, affording 1.7 mg of (+)-**3h** and (+)-**3i** in 84% yield. This mixture was separated by HPLC on a Chiralcel OJ column [semipreparative (1 × 25 cm), flow rate = 2.5 mL/min] eluted with 13% ethanol in hexanes to afford 0.51 mg of (+)-**3h** and 0.37 mg of (+)-**3i** in 19% and 26% yield, respectively. The

retention time for (+)-**3h** is 78.0 min, and for (+)-**3i**, 61.0 min. Data for (+)-**3h**: $[\alpha]_D^{25} = +12.3$ (*c* 0.09, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00−7.95 (m, 2H), 7.25−7.20 (m, 2H), 6.36 (d, 1H, $J = 11.22$ Hz), 5.99 (d, 1H, $J = 11.22$ Hz), 5.32 (br s, 1H), 4.98 (br s, 1H), 4.44−4.30 (m, 1H), 4.23−4.22 (m, 1H), 3.23−3.15 (m, 1H), 3.07−2.97 (m, 1H), 2.66 (br s, 1H), 2.60 (dd, 1H, $J = 3.39$ and 13.26 Hz), 2.30 (dd, 1H, $J = 5.61$ and 13.29 Hz), 2.04−1.88 (m, 4H), 1.81−1.44 (m, 11H), 1.30−1.12 (m, 4H), 0.88 (d, 3H, $J = 6.33$ Hz), 0.50 (s, 3H); due to insufficient amount, ^{13}C NMR was not obtained; IR (neat) 3299 (m), 2926 (s), 2869 (s), 1587 (m), 1491 (w), 1446 (w), 1140 (w), 1350 (m), 1220 (s), 1016 (w), 1057 (w), 994 (m), 836 (w), 752 (s) cm^{-1}; HRMS calcd for $C_{29}H_{40}FNO_3SNa^+$ [M + Na] 524.2605, found 524.2610; UV (MeOH) λ_{max} 263 nm (ϵ 11 096). Data for (+)-**3i**: $[\alpha]_D^{25} = +22.6$ (*c* 0.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00−7.95 (m, 2H), 7.25−7.19 (m, 2H), 6.36 (d, 1H, $J = 11.22$ Hz), 5.99 (d, 1H, $J = 11.31$ Hz), 5.32 (br s, 1H), 4.98 (br s, 1H), 4.45−4.40 (m, 1H), 4.24−4.18 (m, 1H), 3.22−3.00 (m, 2H), 2.80 (dd, 1H, $J = 3.81$ and 11.82 Hz), 2.67 (br s, 1H), 2.59 (dd, 1H, $J = 3.48$ and 13.38 Hz), 2.31 (dd, 1H, $J = 6.36$ and 13.44 Hz), 2.06−1.87 (m, 3H), 1.55−1.41 (m, 13H), 1.29−1.15 (m, 4H), 0.88 (d, 3H, $J = 6.39$ Hz), 0.50 (s, 3H); due to insufficient amount, ^{13}C NMR was not obtained; IR (neat) 3294 (m), 2921 (s),2866 (m), 1583 (m), 1490 (m), 1348 (m), 1222 (s), 1096 (w), 1052 (m), 997 (m), 838 (w), 750 (s) cm^{-1}; HRMS calcd for $C_{29}H_{40}FNO_3SNa^+$ [M + Na] 524.2605, found 524.2619; UV (MeOH) λ_{max} 263 nm (ϵ 10 895).

Sulfoximine Analogue 3j. A flame-dried 5-mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was charged with (*S*)-**13** [7.5 mg, 0.026 mmol; **13** was prepared by treatment of (*S*)-*N*-*tert*-butyldimethylsilyl-*S*-methyl-*S*-phenylsulfoximine with *n*-BuLi in THF at −78 °C followed by *N*-fluorobenzenesulfonimide (NFSI) in 42% yield] and dissolved in 0.5 mL of freshly distilled THF. Then the flask was cooled to −78 °C in a 2-propanol/dry ice bath. To this solution was added 50 mL of LHMDS (0.05 mmol, 1.0 M solution in THF) dropwise over several minutes, resulting in a yellow color. This mixture was allowed to stir at −78 °C for an additional 10 min. Meanwhile, 0.5 mL of THF solution of chlorodiethyl phosphate (4.4 mg, 3.8 μL, 0.026 mmol) was transferred into the flask containing the lithiated sulfoximine at −78 °C via cannula over a few minutes. After the addition was complete, the mixture was stirred at −78 °C for about 1 h. Then, 0.5 mL of a THF solution of aldehyde (+)-**12** (11 mg, 0.002 mmol) was transferred via cannula over a few minutes at −78 °C. The reaction mixture was allowed to warm to room temperature over 2 h. TLC showed almost complete consumption of (+)-**12**. The reaction was quenched by addition of 1 mL of pH 7 buffer and then rinsed into a separatory funnel with ethyl acetate. The mixture was extracted with ethyl acetate (3 × 5 mL). The combined extracts were washed with water (1 × 5 mL) and brine solution (1 × 5 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by preparative TLC plate eluted with 10% ethyl acetate in hexanes to give 7.8 mg of the coupled product in 67% yield.

An argon-purged 5 mL polypropylene vial equipped with a magnetic stir bar along with a cap was charged with the coupled product (7 mg, 0.0083 mmol) dissolved in 0.4 mL of acetonitrile to give ca. 0.02 M solution. To this well-stirred solution was added HF (0.83 mmol, 0.34 mL of 49% aqueous solution) via syringe at room temperature, and the mixture was then allowed to stir at room temperature in the dark for 2 h. TLC showed the completion of the reaction. This reaction mixture was diluted with ether (10 mL) and a saturated solution of $NaHCO_3$ was added until no more carbon dioxide was liberated. The reaction mixture was then rinsed into a separatory funnel with ethyl acetate and was extracted with ethyl acetate (4 × 5 mL). The combined extracts were washed with water (1 × 10 mL) and brine solution (1 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product, which was purified on a preparative TLC plate eluted with 99% ethyl acetate in the presence of 1% triethylamine to afford 3.2 mg of **3j** in 78% yield. This was further purified by HPLC on a (S,S)-Whelk-O1 column [semipreparative (1 × 25 cm), flow rate = 3.0 mL/min] eluted with 20% ethanol in hexanes to afford 0.8 mg of **3j**. The retention time for **3j** is 39.7 min. Data for **3j**: ^1H NMR ($CDCl_3$, 400 MHz): δ 8.04−8.02 (m, 2H), 7.64−7.62 (m, 1H), 7.57−7.52 (m, 2H), 6.35 (d, 1H, $J = 10.4$ Hz), 6.01 (dd, 1H, $J = 11.2$ and 32 Hz), 5.98 (d, 1H, $J = 11.6$ Hz), 5.31 (br s, 1H) 4.96 (br s, 1H), 4.43−4.40 (m, 1H), 4.23−4.22 (m, 1H), 2.83−2.80 (m, 1H), 2.29 (s, 1H), 2.66−2.56 (m, 1H), 2.36−2.28 (m, 1H), 2.04−1.90 (m, 3H), 1.82−1.62 (m, 4H), 1.40−1.25 (m, 9H), 1.09 (d, 3H, $J = 6.8$ Hz), 0.49 (s, 3H); HRMS calcd for $C_{29}H_{38}FNO_3SNa^+$ [M + Na] 522.2448, found 522.2439; UV (MeOH) λ_{max} 266 nm (ϵ 5447).

Preparation of Sulfoximine 14. A flame-dried 10 mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was charged with (+)-*S*-*N*-*tert*-butyldimethylsilyl sulfoximine (43 mg, 0.16 mmol) and dissolved in 1.5 mL of freshly distilled THF. Then the flask was cooled to −78 °C in a 2-propanol/dry ice bath. To this solution was added 0.16 mL of *t*-BuLi (0.18 mmol, 1.1 M solution in pentane) dropwise via syringe over several minutes, resulting in a yellow color. This mixture was allowed to stir at −78 °C for an additional 30 min. To this solution was added diethylchlorophosphate (41.3 mg, 35 mL, 0.24 mmol) via syringe. After the addition was complete, the mixture was stirred at −78 °C for about 1 h. TLC showed that the starting material was entirely consumed. The reaction was quenched by addition of water (5 mL) and then the mixture was rinsed into a separatory funnel and extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with water (1 × 10 mL) and brine solution (1 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product. The crude product was purified by flash chromatography eluted with a 9:1 mixture of ethyl acetate/hexanes to give 34 mg of sulfoximine **14** as an oil in 53% yield. Data for **14**: $[\alpha]_D^{22} = +40.3$ (*c* 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.99−7.97 (m, 2H), 7.58−7.48 (m, 3H), 4.13−4.02 (m, 4H), 3.73 (dd, 1H, $J = 3.6$ and 15.2 Hz), 3.68 (dd, 1H, $J = 3.6$ and 15.2 Hz), 1.28−1.21 (m, 6H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.46, 132.47, 128.55, 127.83, 62.74 (d, $J = 6.1$ Hz), 62.55 (d, $J = 6.1$ Hz), 58.02 (d, $J = 135.8$ Hz), 25.85, 17.96, 16.22 (d, $J = 2.1$ Hz), 16.16 (d, $J = 2.3$ Hz), −2.63, −2.65; IR (neat) 3066 (w), 2955 (m), 2929 (m), 2855 (m), 1473 (m), 1446 (m), 1391 (m), 1361 (m), 1320 (m), 1300 (s), 1253 (s), 1167 (s), 1052 (s), 1025 (s), 974 (m), 834 (s), 778 (m), 689 (m) cm^{-1}; HRMS calcd for $C_{17}H_{32}NO_4PSSiNa^+$ [M + Na] 428.1451, found 428.1435.

Sulfoximine Analogues 3k and 3l. A flame-dried 5 mL recovery flask equipped with a magnetic stir bar and a septum along with an Ar balloon was charged with phosphonate **14** (4.2 mg, 0.01 mmol) dissolved in 0.5 mL of freshly distilled THF. Then the flask was cooled to −78 °C in a 2-propanol/dry ice bath. To this solution was added 13 mL of *t*-BuOK (0.013 mmol, 1.0 M solution in THF) dropwise over several minutes via syringe, resulting in a yellow color. This mixture was then allowed to stir at −78 °C for an additional 30 min. Meanwhile, a flame-dried 5-mL pear-shaped flask equipped with a septum along with an Ar balloon was charged with 22-aldehyde (+)-**12** (5.0 mg, 0.0087 mmol) dissolved in 1.0 mL of freshly distilled THF and cooled to −78 °C in a 2-propanol/dry ice bath. The solution of (+)-**12** was transferred into the flask containing the anion of **14** at −78 °C via cannula over a few minutes. After the addition was complete, the mixture was stirred at −78 °C for about 1 h. Then the flask was warmed to room temperature and allowed to stir for 1.5 h. TLC showed the consumption of the starting material. Reaction was quenched by addition of water (5 mL) and then the mixture was rinsed into a separatory funnel extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with water (1 × 10 mL) and brine solution (1 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product as a 2:1 mixture of isomers (5.0 mg, 0.006 mmol). This mixture was then charged into an argon-purged 5 mL polypropylene vial, equipped with a magnetic stir bar along

with a cap, and dissolved in 0.6 mL of anhydrous acetonitrile to give ca. 0.01 M solution. To this well-stirred solution was added HF (0.6 mmol, 0.25 mL, 49% aqueous solution) via syringe at room temperature, and the mixture was then allowed to stir at room temperature in the dark for 4 h. TLC showed the completion of the reaction. This reaction mixture was diluted with ether (10 mL), and a saturated solution of $NaHCO_3$ was added until no more carbon dioxide was liberated. The reaction mixture was then rinsed into a separatory funnel with ethyl acetate and was extracted with ethyl acetate (3×10 mL). The combined extracts were washed with water (1×10 mL) and brine solution (1×10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated in vacuo to give the crude product, which was passed through a pad of silica gel to afford 2.3 mg of a mixture of **3k** and **3l** in 79% yield. This mixture was separated by HPLC on a Chiralcel OJ column [semipreparative (1×25 cm), flow rate = 2.5 mL/min] eluted with 17% ethyl acetate in hexanes to afford 800 mg of **3k** and 540 mg of **3l** in 28% and 19% yields, respectively. Data for **3k**: $[\alpha]_D^{25} = +7.7$ (*c* 0.069, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96−7.93 (m, 2H), 7.61−7.48 (m, 3H), 6.83 (dd, 1H, J = 8.9 and 15.0 Hz), 6.35 (d, 1H, J = 12.60 Hz), 6.31 (d, 1H, J = 15.00 Hz), 5.98 (d, 1H, J = 10.83 Hz), 5.31 (s, 1H), 4.97 (s, 1H), 4.48−4.38 (m, 1H), 4.28−4.18 (m, 1H), 2.84−2.79 (m, 2H), 2.62−2.57 (m, 1H), 2.34−2.28 (m, 2H), 2.06−1.88 (m, 4H), 1.69−1.33 (m, 7H), 1.33−1.22 (m, 4H), 1.11 (d, 3H, J = 6.6 Hz), 0.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.98, 147.59, 142.22, 133.34, 130.10, 129.15, 127.65, 124.74, 117.74, 114.95, 111.80, 70.80, 66.82, 55.91, 55.46, 46.12, 45.22, 42.83, 40.14, 39.24, 28.91, 27.06, 23.38, 22.22, 19.03, 12.31; IR (neat) 3295 (w), 2931 (m), 2872 (w), 1443 (m), 1414 (w), 1349 (m), 1220 (m), 1055 (m), 979 (m), 750 (m), 685 (m) cm^{-1}; HRMS calcd for $C_{29}H_{39}NO_3SNa^+$ [M + Na] 504.2543, found 504.2530; UV (MeOH) λ_{max} 261 nm (ϵ 12 799). Data for **3l**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96−7.94 (m, 2H), 7.61−7.48 (m, 3H), 6.83 (dd, 1H, J = 89.8 and 15.0 Hz), 6.35 (d, 1H, J = 8.3 Hz), 6.31 (d, 1H, J = 15.00 Hz), 5.98 (d, 1H, J = 11.16 Hz), 5.31 (s, 1H) 4.97 (s, 1H), 4.47−4.38 (m, 1H), 4.28−4.18 (m, 1H), 2.81−2.76 (m, 2H), 2.60−2.57 (m, 1H), 2.34−2.25 (m, 2H), 2.06−1.87 (m, 4H), 1.62−1.37 (m, 7H), 1.33−1.25 (m, 4H), 0.99 (d, 3H, J = 6.6 Hz), 0.42 (s, 3H); due to insufficient amount, ^{13}C NMR was not obtained; HRMS calcd for $C_{29}H_{39}NO_3SNa^+$ [M + Na] 504.2543, found 504.2543; UV (MeOH) λ_{max} 265 nm (ϵ 7718).

Biochemical Studies. A recombinant cell line expressing human CYP24 enzyme (V79-CYP24) was used to measure the inhibitory properties of sulfoximine analogues on the enzyme activity as described before.[6,22,23] Briefly, V79-CYP24 cells (250 000 cells/plate) in 150 μL of medium were incubated with 25 μL of sulfoximine analogue (10^{-6}−10^{-9} M). After 10 min, 25 μL of substrate [^{3}H-1β]-1α,25(OH)$_2$D$_3$ (20 nM) was added and the plate was incubated for 2 h at 37 °C in a humidified atmosphere containing 5% CO_2. Both sulfone analogue and radiolabeled substrate were prepared in Dulbecco's modified Eagle medium (DMEM) with 1% bovine serum albumin (BSA) in the absence and presence of 100 μM 1,2-dianilinoethane, respectively. The reaction was terminated by the addition of 500 μL of methanol and transferred to a glass tube. The aqueous phase was extracted by standard Bligh−Dyer extraction in which we substituted dichloromethane for chloroform.[24] Samples were then spun at 4000 rpm for 5 min. Triplicate 100 μL aliquots of aqueous fraction containing water-soluble CYP24 products were mixed with 600 μL of scintillation fluid and the radioactivity was measured by use of a scintillation counter. All values were normalized for background.

Measurement of Enzyme Activity of CYP27A1. CYP27A1 activity was measured as described by Dilworth et al.[24] with the exception of the use of V79-CYP27A cells. Briefly, each CYP27A assay was performed in 6-well plate format with V79-CYP27A cells at 500 000 cells/well in a final volume of 600 μL of DMEM containing 1% BSA. Solutions containing inhibitors in assay medium were added in a volume of 25 μL to achieve desired final concentrations (10^{-9}−10^{-5} M). The final reaction mixture also contained antioxidant DPPD (Sigma−Aldrich, Milwaukee, WI) at a concentration of 100 nM and substrate 1α -(OH)D$_3$ (Sigma−Aldrich) at a final concentration of 8 μM. After 24 h of incubation at 37 °C, reactions were terminated with the addition of 750 μL of methanol. The reaction mixtures were transferred individually into disposable glass culture tubes and subjected to Bligh−Dyer extraction with dichloromethane and saturated KCl solution. The lipophilic product and substrate were recovered in organic phase, dried, and subjected to HPLC analysis on a SIL 3 μm column in hexane/2-propanol/methanol (91/7/2) isocratic mobile phase. The area under the curve for both substrate and product was used to estimate the conversion rate of 1α-(OH)D$_3$ into calcitriol. The normalized activity for each concentration point of the inhibitors was calculated to quality control samples without inhibition with the conversion for noncell controls subtracted.

Measurement of Enzyme Activity of CYP27B. SW900 cells were plated in 24-well plates at 250 000 cells/well. The cells were washed with 1× PBS followed by addition of 150 μL of actinomycin D (1 μg/mL) in medium per well and incubation for 1 h to halt the RNA transcription. Solutions containing inhibitors in assay medium were added in a volume of 25 μL to achieve desired final concentrations (10^{-9}−10^{-5} M). The final reaction mixture also contained antioxidant DPPD at a concentration of 100 nM and substrate 3H-(23,24)-25-(OH)D$_3$ (103 Ci/mmol) (Amersham, Piscataway, NJ) at a final concentration of 10 nM. After incubation at 37 °C for 5 h, reactions were stopped with the addition of 400 μL of methanol. The reaction mixtures were transferred into Eppendorf tubes and the solutions were dried in a Speed Vac concentrator. The lipophilic substrate and metabolite were extracted in 80 μL of mobile phase by vortexing and sonication. Aliquots (50 μL) of the mobile-phase extract were subjected to HPLC analysis on a SIL 3 μm column in hexane/2-propanol/methanol (91/7/2) isocratic mobile phase on a fully automated Waters Alliance 2695 HPLC system (Milford, MA) and a Radioflow detector LB509 (EG&G Berthold, Bundoora, Australia). The area under the curve for both substrate and product was used to estimate the conversion rate of 25-(OH)D$_3$ into calcitriol. The normalized activity for each concentration point of the inhibitors was calculated to quality control samples without inhibition with the conversion for noncell controls subtracted.

Determination of Urinary Calcium Levels.[15] Male F344 rats (150 g) were housed individually in glass metabolism cages and received food and water ad libitum. After several days of acclimation, each rat received 1 μg/kg of weight of the corresponding sulfoximine analogue per os for 7 consecutive days in 150 μL of propylene glycol/0.05 M Na_2HPO_4 (80:20). Urine samples, which were collected on ice, were centrifuged at 650*g* for 100 min, adjusted to pH 6 as necessary, and assayed for calcium content spectrophotometrically at 575 nm by use of reagents and standards from Sigma calcium kit no. 587.

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