Low-Calcemic, Highly Antiproliferative, 23-Oxa Ether Analogs of the Natural Hormone 1α,25-Dihydroxyvitamin D3: Design, Synthesis, and Preliminary Biological Evaluation

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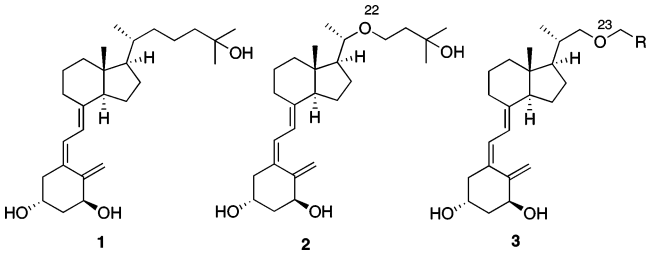
Eight new side-chain allylic, benzylic, and propargylic ether analogs of the natural hormone calcitriol have been rationally designed and easily synthesized. Three of these 23-oxa ether analogs lacking the typical side-chain OH group are more antiproliferative in vitro and desirably less calcemic in vivo than the natural hormone. One of these three 23-oxa analogs has transcriptional potency almost as high as that of calcitriol, even though it binds to the human vitamin D receptor only about 1% as well as calcitriol.

Introduction

Steroid hormones are necessary for good health in humans.[1,2] Over the years, diverse oxa steroids have been prepared to probe how the replacement of a $-CH_2$ group by an O-atom affects biological activity. Significant and valuable biological benefits have been recorded for some oxa steroids: (1) 6-oxa steroids as $GABA_A$ receptor modulators;[3] (2) 7-oxa steroids as potent and selective progesterone receptor antagonists;[4] (3) 11-oxa steroids as progestational agents;[5,6] and (4) 15-oxa steroids as estrogenic agents.[7] Some oxa analogs of the vitamin D seco-steroids have been reported.[8] The most noteworthy oxa analog of the natural hormone 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**) is the Chugai Pharmaceutical Company's maxacalcitol (**2**);[9] this 22-oxa-25-OH analog is currently a clinically used drug for systemic chemotherapy of secondary hyperparathyroidism and is a drug candidate for topical chemotherapy of psoriasis, an intractable skin disease. Some 23-oxa-25-hydroxy analogs of the natural hormone **1** have been studied, but none surpasses or even matches Chugai's drug, 22-oxa-25-hydroxy **2**, in terms of favorable separation of antiproliferative and prodifferentiation activity from unfavorable calcemic activity.[10] For example, in a broad study of structure−activity relationships (SAR) in 23-oxa-25-hydroxy analogs of **1**, the Schering Corporation found that the potential therapeutic window between desirably high antiproliferative or prodifferentiation activity and desirably low calcemic activity was small for 23-oxa calcitriol, 20-ene-23-oxa calcitriol, and 22-ene-25-oxa calcitriol,[10] compared to a big therapeutic window for the Chugai drug, 22-oxa-25-hydroxy **2**.[11] Pursuing our interest in biologically active analogs of the natural hormone **1** that lack the conventional 25-OH group,[12−14] we designed a series of analogs in which the natural 25-OH group is removed and in which the natural 23-CH_2 group is replaced by an oxygen atom. This overall balanced removal of oxygen from position-25 and introduction of oxygen at position-23 has produced some new vitamin D ether analogs with high therapeutic potential. We describe here this new series of very easily synthesized allylic, benzylic, and propargylic ether analogs **3** in which an oxygen atom is located at position-23 on the C,D-ring side chain and, for the first time, in which the standard side-chain terminal −OH group is absent. Despite the absence of this terminal −OH group, thought to be essential for effective binding to the vitamin D receptor (VDR[a]),[15] several of these new 23-oxa ether analogs have high antiproliferative activity in vitro and desirably low calciuric activity in vivo.



Chemistry

Inexpensive vitamin D_2 has been fragmented and converted into C,D-ring building block C-22 alcohol **4**.[16] Starting with this C,D-ring C-22 alcohol **4** as nucleophile, Williamson ether coupling and C-8 desilyation produced 23-oxa ethers **6a**−**6f** and **6h** in 30−85% yields (Scheme 1). 23-Oxa ether **6g** was not successfully formed in this way. 23-Oxa ether **6g**, however, was formed in 82% using a Williamson ether coupling but starting with electrophilic C,D-ring C-22 iodide[17] and furfuryl alcohol. Oxidation of **6a**−**6h** with pyridinium dichromate produced C-8 ketones **7a**−**7h** in >75% yields. Coupling of C-8 ketones with the known[18] A-ring lithiophosphine oxide (−)-**8** and then desilylation afforded the desired 23-oxa ether analogs KSP-23-oxa-25-CH_2-26TB (**3a**), KSP-23-oxa-25-ene-26-TB (**3b**), KSP-23-oxa-25-C(CH_2)-MeCyclohex (**3c**), KSP-23-oxa-CH_2Me_2-cyclohexene (**3d**), KSP-23-oxa-25-C(CH_2)-Ph (**3e**), KSP-23-oxa-24-CH_2Ph (**3f**), KSP-23-oxa-furfuryl (**3g**), and KSP-23-oxa-25-yne-TB (**3h**) in 10−65% yields (low yields on weakly antiproliferative compounds were not optimized). The convergent nature of synthetic Scheme 1 and the relatively small number of chemical steps between starting materials and target analog suggest that large scale manufacture of a lead drug candidate should be feasible and economically favorable. All of these 23-oxa analogs (without the natural 25-OH group)

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[a] Abbreviations: VDR, vitamin D receptor.

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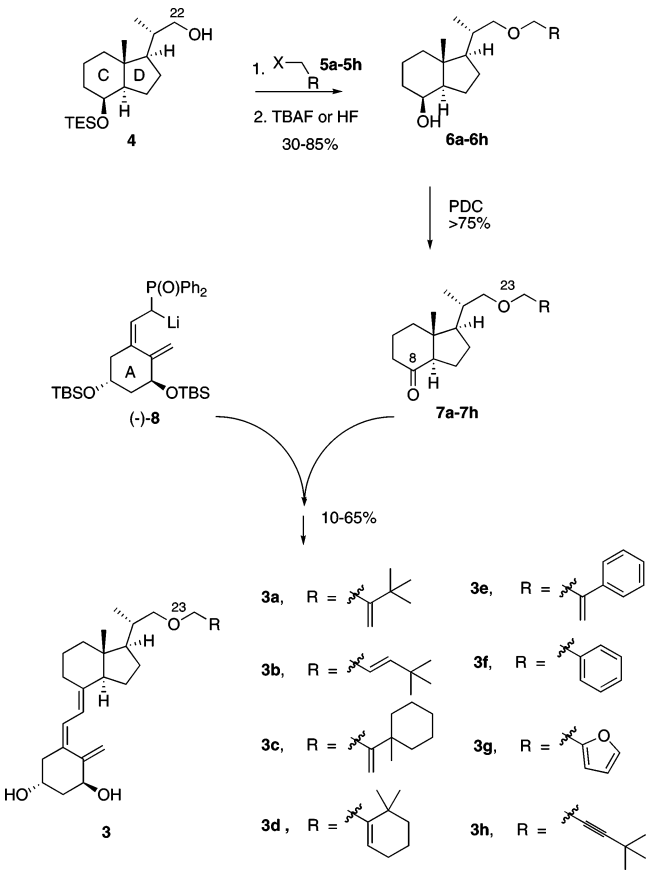
Table 1.

analog	antiproliferative IC_{50} (nM)	transcriptional activity ED_{50} (nM)	competitive VDR binding IC_{50} (nM)	calciuria activity compared to **1**	Log P
1	80	1.5	0.8	1	3.6
3a	20	6	85	<0.02	4.7
3b	400	[a]	[a]	[a]	4.9
3c	100	350	198	<0.02	5.3
3d	50	52	300	<0.02	4.9
3e	400	[a]	[a]	[a]	5.1
3f	180	410	63	<0.02	4.4
3g	600	[a]	[a]	[a]	3.3
3h	2	40	47	<0.02	4.6

[a] Not tested due to relatively modest antiproliferative activity.

Scheme 1



except furan analog **3g** are more lipophilic (higher log P) than the natural hormone **1** (Table 1).

Biology

A standard in vitro protocol[19] for determining antiproliferative activity of new analogs **3a**−**3h** in murine keratinocytes produced the data shown in Table 1. Noteworthy is the exceptionally high antiproliferative potency of allylic ether analogs **3a** and **3d** and especially of propargylic ether analog **3h** (Table 1). Propargylic ether analog **3h**, with an IC_{50} of 2 nM, is approximately 40 times more antiproliferative than the natural hormone **1** (IC_{50} = 80 nM).

A standard protocol[20] using a recombinant human VDR and a reporter gene containing a vitamin D response element (VDRE) gave the transcriptional potencies of 23-oxa analog **3a**−**3h**, as shown in Table 1. Noteworthy is the very high transcriptional potency of allylic ether **3a** (ED_{50} = 6 nM), approaching that of **1** (ED_{50} = 1.5 nM).

A standard assay[20] for competitive binding to the human VDR generated the IC_{50} values shown in Table 1. Noteworthy is that allylic ether **3a** binds to the human VDR only about 1% as well as natural hormone **1** but, nevertheless, is almost as transcriptionally potent and is more antiproliferative than **1**. Noteworthy also is that propargylic ether **3h** binds to the human VDR only twice as well as allylic ether **3a** but is approximately ten times more antiproliferative than **3a**.[21]

A standard in vivo[22] assay probed the calciuric activity of these new 23-oxa analogs. Remarkably, 23-oxa allylic ethers **3a** and **3d** and 23-oxa propargylic ether **3h** are at least 50 times less calciuric than **1** (Figure 1). Thus, the 23-oxa allylic ether **3a** lacking a 25-OH group has a substantial therapeutic window, and the 23-oxa propargylic ether **3h** also lacking a 25-OH group has an even better therapeutic window, comparing favorably to that of the Chugai drug[9,11] 22-oxa-25-hydroxy **2**. Gene regulation studies in vivo showed a strong induction of CYP24 mRNA by compounds **1**, **3a**, and **3d**, as well as upregulation of TRPV6 mRNA (Figure 2). These results indicate that the two new ether analogs **3a** and **3d** are transcriptionally active in vivo and, therefore, it is not likely that their low calcemic activity is due to a very short half-life or to rapid catabolism.

It is expected that in vivo catabolism (hydroxylation)[23] of this series of 23-oxa analogs by cytochrome P-450 enzymes will occur mainly at C-24 due to the radical-stabilizing effect of the 23-oxygen atom and to the radical-stabilizing effect also of the adjacent olefinic or acetylenic multiple bond. Because such allylic or propargylic radical intermediates would be stabilized by resonance delocalization, they are expected to be formed more easily than in saturated 23-oxa side-chain analogs. Thus, the in vivo half-lives of 23-oxa allylic ethers **3a** and **3d** and of propargylic ether **3h** are expected to be shorter than that of the natural hormone **1**, leading in all three cases to side-chain fragmentation and formation of the same 22-CH_2−OH alcohol that is only weakly antiproliferative in vitro (data not shown). An analog having a relatively short half-life in vivo may represent a therapeutic advantage, as is the case for the topically-used antipsoriasis drug calcipotriol.[24]

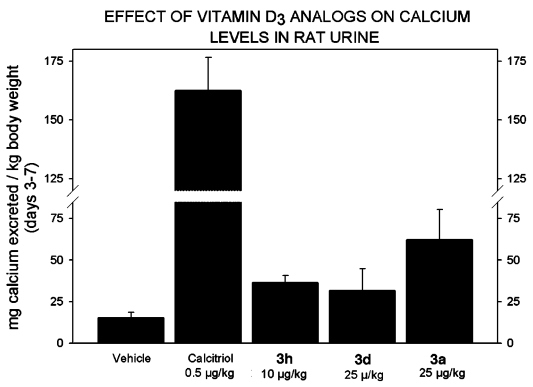


Figure 1. Calciuric activity in vivo of ether analogs **3a**, **3d**, and **3h**.

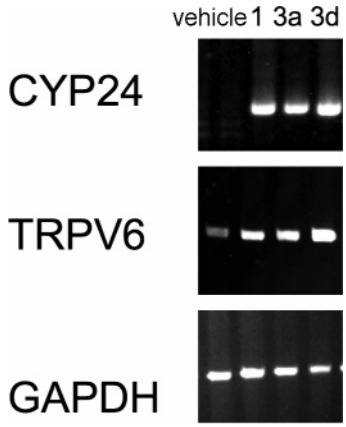


Figure 2. Transcriptional activity in vivo of ether analogs **3a** and **3d:** CYP24 and TRPV6 mRNA levels in the duodenum of female mice were determined by semiquantitative RT-PCR, 4 h after injection of vehicle, calcitriol (**1**), analog **3a**, and analog **3d**. Shown is a representative ethidium bromide-stained gel with the amplified gene products.

Conclusions

Three of these new lipophilic analogs of **1** possess a very desirable therapeutic profile of high antiproliferative activity and desirably low calcemic activity. Of these three, 23-oxa allylic ether **3a** and especially 23-oxa propargylic ether **3h** feature the best combination of structural features leading to high antiproliferative activity and low calcemic activity. Based on these promising results, further evaluation of the pharmacological properties and the medical potential of these easily and convergently synthesized 23-oxa vitamin D new chemical entities is appropriate and timely.

Experimental Section[25]

Log P values were calculated using ChemAxon's Marvin and calculator plugin demo. The purity of analogs **3a**−**3h** was judged to be ≥96% based on HPLC analysis.

C-8 Alcohol 6a. To ice-cooled hexanes-washed KH (55 mg of a 30% suspension in mineral oil, 0.41 mmol) was added a solution of alcohol **4** (45 mg, 0.14 mmol) in THF (2.5 mL). The mixture was stirred at rt for 45 min until a light yellow color developed. Tosylate **5a**[26] (111 mg, 0.41 mmol) and Bu_4NI (3 mg, 0.01 mmol) were added to the reaction flask and the mixture was stirred at rt for 14 h. The reaction was quenched by addition of water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (5% ethyl acetate in hexanes) to afford 57 mg of crude TES-protected alcohol **6a**. The crude TES-protected alcohol was dissolved in THF (2 mL) and TBAF (0.16 mL of a 1 M solution in THF) was added. The solution was stirred overnight before being quenched with water. The mixture was extracted with dichloromethane (3 × 5 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography afforded 25 mg of the alcohol as a colorless oil in 60% yield. $[\alpha]_D^{26}$ +23.5 (*c* 0.43, $CHCl_3$); IR (neat, cm^{-1}) 3436 (br), 3087 (w), 1636 (w), 1458 (m), 1361 (m), 1264 (w), 1202 (w), 1167 (w), 1095 (s), 991 (w), 944 (w), 905 (m), 857 (w), 724 (w); ^1H NMR ($CDCl_3$, 100 MHz) δ 5.06 (m, 1H), 4.98 (m, 1H), 4.08 (m, 1H), 3.96 (m, 2H), 3.39 (dd, 1H, J = 8.8, 3.6 Hz), 3.13 (dd, 1H, J = 8.8, 7.2 Hz), 2.00 (m, 1H), 1.88−1.10 (m, 14H), 1.09 (s, 9H), 1.04 (d, 3H, J = 6.4 Hz), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.99, 108.43, 75.63, 71.43, 69.29, 53.51, 52.34, 41.91, 40.20, 36.45, 34.76, 33.57, 29.41, 26.75, 22.59, 17.49, 17.39, 13.55; HRMS calcd for $C_{20}H_{36}O_2$ [MH^+], 309.27936; found, 309.27804.

C-8 Ketone 7a. A solution of alcohol **6a** (14 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) was cannulated into a reaction vessel equipped with PDC (49 mg, 0.13 mmol) and oven-dried Celite (45 mg). After stirring overnight, the mixture was filtered, and the filtrate was concentrated in vacuo and purified by column chromatography (10−25% ethyl acetate in hexanes) to afford 13 mg of **7a** as a colorless oil in 95% yield. $[\alpha]_D^{24}$ +2.1 (*c* 0.625, $CHCl_3$); IR (neat, cm^{-1}) 2960 (s), 2972 (m), 1715 (s), 1461 (w), 1384 (w), 1361 (w), 1098 (m), 1055 (w), 903 (w); ^1H NMR ($CDCl_3$, 100 MHz) δ 5.06 (m, 1H), 4.98 (m, 1H), 4.08 (m, 1H), 3.96 (m, 2H), 3.39 (dd, 1H, J = 8.8, 3.6 Hz), 3.14 (dd, 1H, J = 8.8, 7.2 Hz), 2.00 (m, 1H), 1.88−1.20 (m, 11H), 1.09 (s, 9H), 1.04 (d, 3H, J = 6.4 Hz), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.08, 211.91, 76.54, 72.03, 61.66, 53.24, 49.90, 42.85, 40.94, 38.77, 36.60, 27.06, 26.26, 24.01, 19.16, 17.52. 12.48; HRMS calcd for $C_{20}H_{34}O_2Na^+$ [M + Na], 329.2451; found, 329.2446.

Analog 3a. Enantiomerically pure phosphine oxide (−)-**8**[17] and C,D-ring ketone **7a** were separately azeotropically dried with anhydrous benzene (4 × 5 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 an Ar ballon was charged with phosphine oxide (−)-**8** (52 mg, 0.09 mmol). The reagent was dissolved in 2.0 mL of freshly distilled THF and cooled to −78 °C. To this solution *n*-BuLi (58 μL, 0.09 mmol, 1.60 M solution in hexanes) was added 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 flask containing C,D-ring ketone **7a** (12.5 mg, 0.04 mmol) was dissolved in 0.75 mL of freshly distilled THF and cooled to −78 °C. The solution of C,D-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 6 h. Upon observation of a light yellow color, the reaction was quenched with 5 mL of pH 7 buffer and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a crude product that was purified by column chromatography (5−50% ethyl acetate in hexanes), affording 16.0 mg of product in a 59% yield. The protected analog was dissolved in CH_3CN (2 mL) and HF (49%, 0.1 mL) was added. After stirring 1 h, the reaction was quenched with a saturated solution of $NaHCO_3$, extracted with ethyl acetate (3 × 10 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (50−75% ethyl acetate in hexanes with 1% NEt_3) to afford 8 mg of analog **3a** as an oil in 80% yield. HPLC purification afforded 1.2 mg pure **3a**. $[\alpha]_D^{25}$ +23.9 (*c* 0.05, $CHCl_3$); IR (neat, cm^{-1}) 3365 (brs), 2927 (s), 2856 (m), 1456 (w), 1056 (w), 906 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.37 (d, 1H, J = 11.2 Hz), 6.02 (d, 1H, J = 11.2 Hz), 5.32 (m, 1H), 5.06 (m, 1H), 4.99 (m, 2H), 4.42 (m, 1H), 4.22 (m, 1H), 3.96 (m, 2H), 3.40 (dd, 1H, J = 8.8, 3.2 Hz), 3.14 (dd, 1H, J = 8.8, 7.6 Hz), 2.82 (dd, 1H, J = 11.6, 3.6 Hz), 2.59 (dd, 1H, J = 13.2, 3.2 Hz), 2.31 (dd, 1H, J = 13.6, 6.8 Hz), 2.04−1.24 (m, 16H), 1.09 (s, 9H), 1.06 (d, 3H, J = 6.8 Hz), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.00, 147.66, 143.06, 132.95, 124.95, 117.05, 111.74, 108.49, 75.70, 71.47, 70.80, 66.84, 56.08, 53.44, 46.02, 45.26, 42.87, 40.33, 37.28, 34.79, 29.44, 29.08, 27.25, 23.56, 22.38, 17.77, 12.04; HRMS calcd for $C_{29}H_{46}O_3Na^+$ [M + Na], 465.3339; found, 465.3363. UV (MeOH) λ_{max} 265 nm (ϵ 10 861).

C-8 Ketone 7b. To ice-cooled hexanes-washed KH (82 mg of a 30% suspension in mineral oil, 0.62 mmol) was added a solution of **4** (40 mg, 0.12 mmol) in THF (2.5 mL). The mixture was stirred at rt for 45 min until a light yellow color developed. Tosylate **5b**[27] (250 mg, 0.60 mmol) was added to the reaction flask and the mixture was stirred at rt for 14 h. The reaction was quenched by addition of water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give crude TES-protected alcohol. The crude TES-protected alcohol was dissolved in THF (2 mL) and TBAF (0.6 mL of a 1 M solution in THF) was added. The solution was stirred overnight before being quenched with water. The mixture

was extracted with dichloromethane (3 × 5 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (15% EtOAc in hexanes) afforded 27 mg of alcohol **6b** as a colorless oil in 71% yield for the two steps. $[\alpha]_D^{21}$ +33.0 (*c* 0.325, $CHCl_3$); IR (neat, cm^{-1}) 3479 (br), 2963 (s), 2868 (m), 1651 (w), 1620 (w), 1458 (w), 1360 (w), 1265 (w), 1233 (w), 1164 (w), 1109 (w), 1095 (w), 1066 (w), 992 (w), 972 (w), 942 (w), 915 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.68 (td, 1H, *J* = 15.6, 1.2 Hz), 5.44 (td, 1H, *J* = 15.6, 6 Hz), 4.08 (m, 1H), 3.89 (dq, 2H, 6, 1.2 Hz), 3.85 (dd, 1H, 9.2, 3.2 Hz), 3.08 (dd, 1H, 9.2, 7.6 Hz), 1.99 (m, 1H), 1.84−1.07 (m, 13H), 1.02 (m, 12H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.87, 121.40, 74.97, 72.01, 69.31, 53.54, 52.34, 41.94, 40.19, 36.26, 33.59, 29.47, 26.69, 22.60, 17.42, 17.40, 13.57.

A solution of alcohol **6b** (30 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) was cannulated into a reaction vessel equipped with PDC (105 mg, 0.28 mmol) and oven-dried Celite (108 mg). After stirring overnight, the mixture was filtered and the filtrate was concentrated in vacuo and purified by column chromatography (10−25% ethyl acetate in hexanes) to afford 28 mg of **7b** as a colorless oil in 93% yield. $[\alpha]_D^{22}$ +5.1 (*c* 0.50, $CHCl_3$); IR (neat, cm^{-1}) 2958 (s), 2870 (m), 1715 (s), 1461 (w), 1362 (w), 1308 (w), 1240 (w), 1218 (w), 1107 (m), 1056 (w), 974 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.67 (td, 1H, *J* = 15.6, 1.2 Hz), 5.43 (td, 1H, *J* = 15.6, 6 Hz), 3.88 (dq, 2H, *J* = 6, 1.2 Hz), 3.36 (d, 1H, *J* = 9.2, 3.2 Hz), 3.12 (dd, 1H, *J* = 9.2, 7.2 Hz), 2.44 (dd, 1H, *J* = 11.6, 7.6 Hz), 2.31−1.21 (m, 11H), 1.08 (m, 4H), 1.01 (s, 9H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.91, 145.02, 121.24, 74.67, 72.06, 61.66, 53.50, 49.92, 40.95, 38.77, 36.43, 32.87, 29.45, 27.00, 24.02, 19.14, 17.62, 12.49; HRMS calcd for $C_{20}H_{34}O_2$ [MH^+], 307.2637; found, 307.2631.

Analog 3b. Enatiomerically pure phosphine oxide (−)-**8** and C,D-ring ketone **7b** were separately azeotropically dried with anhydrous benzene (4 × 5 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 an Ar balloon was charged with phosphine oxide (−)-**8** (45 mg, 0.077 mmol). The reagent was dissolved in 2.0 mL of freshly distilled THF and cooled to −78 °C. To this solution *n*-BuLi (48 μL, 0.07 mmol, 1.60 M solution in hexanes) was added 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 flask containing C,D-ring ketone **7b** (14 mg, 0.046 mmol) was dissolved in 0.75 mL of freshly distilled THF and cooled to −78 °C. The solution of C,D-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 1 h. Upon observation of a light yellow color, the reaction was quenched with 5 mL of pH 7 buffer and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a crude product that was purified by column chromatography (5% ethyl acetate in hexanes with 1% NEt_3), affording 4 mg of product in a 13% yield. The protected analog was dissolved in THF (2 mL) and TBAF (1.6 M in THF, 30 μL) was added. After stirring overnight, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (50−75% ethyl acetate in hexanes with 1% NEt_3) to afford 2 mg of analog **3b** as an oil (77% yield). $[\alpha]_D^{21}$ +22.7 (*c* 0.07, $CHCl_3$); IR (neat, cm^{-1}) 3299 (br), 2961 (s), 2922 (s), 2850 (s), 1730 (w), 1608 (w), 1470 (w), 1358 (w), 1261 (w), 1202 (w), 1055 (m), 1013 (m), 724 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.38 (d, 1H, *J* = 11.2 Hz), 6.02 (d, 1H, *J* = 11.2 Hz), 5.68 (d, 1H, *J* = 15.6 Hz), 5.45 (td 1H, *J* = 15.6, 6 Hz), 5.32 (m, 1H), 5.00 (m, 1H), 4.43 (m, 1H), 4.23 (m, 1H), 3.90 (m, 2H), 3.39 (dd, 1H, *J* = 9.2, 3.2 Hz), 3.08 (t, 1H, *J* = 8.4 Hz), 2.82 (m, 1H), 2.60 (m, 1H), 2.31 (m, 1H), 2.05−0.83 (m, 29 H) 0.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ147.64, 144.90, 143.11, 132.89, 124.98, 121.39, 117.04, 111.77, 75.01, 72.01, 70.84, 66.86, 56.05, 53.43, 46.02, 45.27, 42.86, 40.30, 37.08, 32.89, 29.48, 29.08, 27.18, 23.55, 22.37, 17.68, 12.04; HRMS calcd for $C_{29}H_{46}O_3$ [M^+], 442.3447; found, 442.3439. UV (MeOH) λ_{max} 264 nm (ε 10 067).

C-8 Alcohol 6c. To ice-cooled hexanes-washed KH (45 mg of a 30% suspension in mineral oil, 0.34 mmol) was added a solution of **4** (37 mg, 0.113 mmol) in THF (2 mL). The mixture was stirred at rt for 1.5 h until a light yellow color developed. Bromide **5c**[28] (74 mg, 0.34 mmol) was added to the reaction flask and the mixture was stirred at rt for 14 h. The reaction was quenched by addition of water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (5% ethyl acetate in hexanes) to afford 42 mg of crude TES-protected alcohol. The crude TES-protected alcohol was dissolved in THF (2 mL) and TBAF (0.27 mL of a 1 M solution in THF) was added. The solution was stirred overnight before being quenched with water. The mixture was extracted with dichloromethane (3 × 5 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (10% EtOAc in hexanes) afforded 23 mg of alcohol **6c** as a colorless oil in 59% yield. $[\alpha]_D^{21}$ +28.5 (*c* 1.15, $CHCl_3$); IR (neat, cm^{-1}) 3421 (brs), 2930 (s), 2861 (m), 1456 (w), 1093 (m), 905 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.18 (d, 1H, *J* = 0.8 Hz), 4.99 (s, 1H), 4.08 (s, 1H), 3.92 (q, 2H, *J* = 5.6 Hz), 3.39 (dd, 1H, *J* = 8.8, 3.2 Hz), 3.13 (t, 1H, *J* = 8.8 Hz), 2.00 (m, 1H), 1.87−1.14 (m, 23 H), 1.05−0.99 (m, 6H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.43, 109.66, 75.74, 71.38, 69.31, 53.52, 52.34, 41.92, 40.21, 38.00, 36.48, 36.44, 36.41, 33.57, 26.77, 26.30, 22.60, 22.48, 17.51, 17.40, 13.56, 6.57, 5.77; HRMS calcd for $C_{23}H_{40}O_2$ [MH^+], 349.3107; found, 349.3082.

C-8 Ketone 7c. A solution of alcohol **6c** (22 mg, 0.063 mmol) in CH_2Cl_2 (2 mL) was cannulated into a reaction vessel equipped with PDC (68 mg, 0.18 mmol) and oven-dried Celite (70 mg). After stirring overnight, the mixture was filtered and the filtrate was concentrated in vacuo and purified by column chromatography (10−25% ethyl acetate in hexanes) to afford 19 mg of **7c** as a colorless oil in 90% yield. $[\alpha]_D^{22}$ +5.4 (*c* 0.40, $CHCl_3$); IR (neat, cm^{-1}) 2930 (s), 2855 (m), 1715 (s), 1455 (w), 1097 (w), 942 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.18 (d, 1H, *J* = 0.8 Hz), 4.99 (s, 1H), 3.93 (m, 2H), 3.39 (dd, 1H, *J* = 8.8, 3.2 Hz), 3.18 (dd, 1H, *J* = 8.8, 6.8 Hz), 2.45 (dd, 1H, *J* = 11.2, 7.2 Hz), 2.24 (m, 2H), 2.13 (m, 1H), 2.01−1.24 (m, 19H), 1.09 (d, 3H, 6.4 Hz), 1.03 (s, 3H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.01, 152.37, 109.73, 75.50, 71.47, 61.70, 53.52, 49.95, 40.97, 38.81, 38.01, 36.66, 36.41, 27.60, 27.10, 26.29, 24.04, 22.48, 19.17, 17.73, 12.51; HRMS calcd for $C_{23}H_{38}O_2$ [MH^+], 397.2950; found, 397.2956.

Analog 3c. Enantiomerically pure phosphine oxide (−)-**8** and C,D-ring ketone **7c** were separately azeotropically dried with anhydrous benzene (4 × 5 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 an Ar balloon was charged with phosphine oxide (−)-**8** (35 mg, 0.06 mmol). The reagent was dissolved in 2.0 mL of freshly distilled THF and cooled to −78 °C. To this solution *n*-BuLi (38 μL, 0.06 mmol, 1.60 M solution in hexanes) was added 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 flask containing C,D-ring ketone **7c** (9 mg, 0.026 mmol) was dissolved in 0.75 mL of freshly distilled THF and cooled to −78 °C. The solution of C,D-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 3 h. Upon observation of a light yellow color, the reaction was quenched with 5 mL of pH 7 buffer and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give crude product that was purified

by column chromatography (5% ethyl acetate in hexanes with 1% NEt_3), affording 9.4 mg of product in a 52% yield. The protected analog was dissolved in THF (2 mL) and TBAF (1.0 M in THF, 70 μL) was added. After stirring overnight, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (50−75% ethyl acetate in hexanes with 1% NEt_3) to afford 4.6 mg of analog **3c** as an oil (77% yield). $[\alpha]_D^{22}$ +29.4 (*c* 0.225, $CHCl_3$); IR (neat, cm^{-1}) 3365 (brs), 2927 (s), 2856 (m), 1456 (w), 1056 (w), 906 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.38 (d, 1H, J = 11.6 Hz), 6.02 (d, 1H, J = 11.2 Hz), 5.33 (t, 1H, J = 1.6 Hz), 5.19 (d, 1H, J = 1.6 Hz), 5.00 (m, 2H), 4.43 (m, 1H), 4.24 (m, 1H), 3.93 (m, 2H), 3.41 (dd, 1H, J = 8.8, 3.6 Hz), 3.14 (dd, 1H, J = 8.8, 7.6 Hz), 2.83 (dd, 1H, J = 12.4, 4.4 Hz), 2.60 (dd, 1H, J = 13.2, 3.2 Hz), 2.31 (dd, 1H, J = 13.2, 6.8 Hz), 2.05−1.22 (m, 26H), 1.09 (d, 3H, J = 8 Hz), 1.03 (s, 3H), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.44, 147.63, 143.13, 132.88, 124.99, 117.02, 111.77, 109.69, 75.80, 71.40, 70.82, 66.86, 56.07, 53.42, 46.02, 45.25, 42.85, 40.32, 38.02, 37.30, 36.45, 36.43, 29.70, 29.08, 27.60, 27.26, 26.31, 23.56, 22.50, 22.38, 17.77, 12.04; HRMS calcd for $C_{32}H_{50}O_3$ [M^+], 482.3760; found, 482.3765. UV (MeOH) λ_{max} 263 nm (ϵ 16 719).

C-8 Alcohol 6d. To ice-cooled hexanes-washed KH (21 mg of a 30% suspension in mineral oil, 0.16 mmol) was added a solution of **4** (26 mg, 0.08 mmol) in THF (2 mL). The mixture was stirred at rt for 1.5 h until a light yellow color developed. Iodide **5d**[29] (40 mg, 0.16 mmol) was added to the reaction flask and the mixture was stirred at rt for 14 h. The reaction was quenched by addition of water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (2% ethyl acetate in hexanes) to afford 19 mg of crude TES-protected alcohol. The crude TES-protected alcohol was dissolved in THF (2 mL) and HF (0.50 mL, 1.2 mmol) was added. The solution was stirred 2 h before being quenched with a satd solution of $NaHCO_3$. The mixture was extracted with ethyl acetate (3 × 5 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (15% EtOAc in hexanes) afforded 8 mg of alcohol **6d** as a colorless oil in 32% yield for the two steps. $[\alpha]_D^{21}$ +40.9 (*c* 0.35, $CHCl_3$); IR (neat, cm^{-1}) 3433 (brs), 2930 (s), 2867 (m), 1474 (w), 1359 (w), 1093 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.64 (m, 1H), 4.08 (m, 1H), 3.87 (m, 1H), 3.36 (dd, 1H, J = 9.2, 3.2 Hz), 3.08 (dd, 1H, J = 8.8, 7.6 Hz), 2.04−1.24 (m, 20 H), 1.05 (d, 6H, J = 1.6 Hz), 1.03 (d, 3H, J = 6.8 Hz), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.02, 74.72, 73.31, 69.32, 58.32, 53.59, 52.51, 41.71, 39.79, 35.22, 33.56, 30.97, 27.41, 26.63, 22.36, 17.44, 17.22, 13.89; HRMS calcd for $C_{22}H_{38}O_2$ [$M - H^+$], 333.2784; found, 333.2788.

C-8 Ketone 7d. A solution of alcohol **6d** (8 mg, 0.024 mmol) in CH_2Cl_2 (2 mL) was cannulated into a reaction vessel equipped with PDC (26 mg, 0.069 mmol) and oven-dried Celite (25 mg). After stirring overnight, the mixture was filtered and the filtrate was concentrated in vacuo and purified by column chromatography (10% ethyl acetate in hexanes) to afford 7.4 mg of **7d** as a colorless oil in 93% yield. $[\alpha]_D^{22}$ +4.3 (*c* 0.30, $CHCl_3$); IR (neat, cm^{-1}) 2961 (s), 2931 (s), 2869 (m), 1714 (s), 1453 (w), 1361 (w), 1147 (w), 1087 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.63 (m, 1H), 3.87 (m, 2H), 3.36 (dd, 1H, J = 9.2, 3.2 Hz), 3.13 (dd, 1H, J = 9.2, 7.2 Hz), 2.45 (dd, 1H, J = 11.6, 7.6 Hz), 2.24 (m, 2H), 2.12 (m, 1H), 2.04−1.35 (m, 15H), 1.08 (d, 3H, J = 6.4 Hz), 1.05 (s, 6H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.87, 141.42, 124.42, 75.25, 72.61, 61.74, 53.62, 49.96, 40.98, 39.59, 38.86, 36.64, 33.07, 28.25, 28.19, 27.13, 25.67, 24.05, 19.21, 19.06, 17.78, 12.53; HRMS calcd for $C_{22}H_{36}O_2$ [MH^+], 333.2794; found, 333.2788.

Analog 3d. Enantiomerically pure phosphine oxide (−)-**8** and C,D-ring ketone **7d** were separately azeotropically dried with anhydrous benzene (4 × 5 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 an Ar balloon was charged with phosphine oxide (−)-**8** (40 mg, 0.069 mmol). The reagent was dissolved in 2.0 mL of freshly distilled THF and cooled to −78 °C. To this solution *n*-BuLi (42 μL, 0.063 mmol, 1.50 M solution in hexanes) was added 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 flask containing C,D-ring ketone **7d** (6 mg, 0.018 mmol) was dissolved in 0.75 mL of freshly distilled THF and cooled to −78 °C. The solution of C,D-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 8 h. Upon observation of a light yellow color, the reaction was quenched with 5 mL of pH 7 buffer and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give a crude product that was purified by column chromatography (5% ethyl acetate in hexanes with 1% NEt_3), affording 10 mg of product in an 80% yield. The protected analog was dissolved in THF (2 mL) and TBAF (1.0 M in THF, 140 μL) was added. After stirring overnight, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (50−75% ethyl acetate in hexanes with 1% NEt_3) to afford 4.0 mg of analog **3d** as an oil (61% yield). $[\alpha]_D^{21}$ +23.4 (*c* 1.0, $CHCl_3$); IR (neat, cm^{-1}) 3378 (brs), 2924 (s), 2848 (m), 1733 (w), 1463 (w), 1427 (w), 1095 (w), 800 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.38 (d, 1H, J = 11.2 Hz), 6.02 (d, 1H, J = 11.2 Hz), 5.64 (m, 1H), 5.33 (m, 1H), 5.00 (m, 1H), 4.43 (m, 1H), 4.23 (m, 1H), 3.87 (m, 2H), 3.37 (dd, 1H, J = 9.2, 3.2 Hz), 3.08 (dd, 1H, J = 9.2, 8.0 Hz), 2.82 (dd, 1H, J = 12.8, 4.8 Hz), 2.60 (dd, 1H, J = 13.6, 3.6 Hz), 2.31 (dd, 1H, J = 13.2, 6.4 Hz), 2.05−1.25 (m, 22H), 1.05 (m, 9H), 0.56 (s, 3H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.63, 143.14, 141.46, 132.87, 125.00, 124.31, 117.02, 111.76, 75.54, 72.48, 70.83, 66.86, 56.08, 53.45, 46.03, 45.26, 42.86, 40.32, 39.57, 37.26, 33.06, 29.08, 28.26, 28.17, 27.28, 25.66, 23.56, 22.39, 19.05, 17.81, 12.04; HRMS calcd for $C_{31}H_{48}O_3$ [M^+], 468.3604; found, 468.3519. UV (MeOH) λ_{max} 264 nm (ϵ 17 342)

C-8 Ketone 7e. To ice-cooled hexanes-washed KH (74 mg of a 30% suspension in mineral oil, 0.55 mmol) was added a solution of **4** (60 mg, 0.18 mmol) in THF (2 mL). The mixture was stirred at rt for 1.5 h until a light yellow color developed. Bromide **5e**[30] (110 mg, 0.55 mmol) was added to the reaction flask and the mixture was stirred at rt for 14 h. The reaction was quenched by addition of water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (2% ethyl acetate in hexanes) to afford 75 mg of the crude TES-protected alcohol. The crude TES-protected alcohol was dissolved in THF (2 mL) and HF (100 μL, 2.4 mmol) was added. The solution was stirred 2 h before being quenched with a satd solution of $NaHCO_3$. The mixture was extracted with ethyl acetate (3 × 5 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (15% EtOAc in hexanes) afforded 46 mg of alcohol **6e** as a colorless oil in 76% yield for the two steps. $[\alpha]_D^{25}$ +30.6 (*c* 2.225, $CHCl_3$); IR (neat, cm^{-1}) 3457 (brs), 2947 (m), 2864 (m), 1444 (w), 1117 (w), 1091 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46 (m, 2H), 7.29 (m, 3H), 5.50 (m, 1H), 5.32 (m, 1H), 4.33 (dq, 2H, J = 13.2, 0.8 Hz), 4.06 (m, 1H), 3.42 (dd, 1H, J = 9.2, 3.6 Hz), 3.19 (dd, 1H, J = 9.2, 7.2 Hz), 1.97 (m, 1H), 1.86−1.11 (m, 13H), 0.97 (d, 3H, J = 6.8 Hz), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.66, 138.94, 128.21, 127.62, 126.11, 113.78, 75.29, 72.94, 69.25, 53.40, 52.33, 41.89, 40.18, 36.30, 33.58, 26.67, 22.57, 17.39, 13.52.

A solution of alcohol **6e** (23 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) was cannulated into a reaction vessel equipped with PDC (76 mg, 0.201 mmol) and oven-dried Celite (75 mg). After stirring overnight, the mixture was filtered and the filtrate was concentrated in vacuo and purified by column chromatography (15% ethyl acetate in hexanes) to afford 20 mg of **7e** as a colorless oil in 87% yield.

$[\alpha]_D^{25}$ +3.8 (*c* 0.70, $CHCl_3$); IR (neat, cm^{-1}) 2955 (m), 2871 (m), 1713 (s), 1458 (w), 1383 (w), 1219 (w), 1094 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 2H), 7.31 (m, 3H), 5.51 (m, 1H), 5.32 (m, 1H), 4.34 (dq, 2H, J = 12.8, 0.8 Hz), 3.42 (dd, 1H, J = 9.2, 3.2 Hz), 3.24 (dd, 1H, J = 9.2, 6.8 Hz), 2.41 (m, 1H) 2.27−1.30 (m, 12 H), 1.03 (d, 3H, J = 6.8 Hz), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.87, 144.60, 138.86, 128.25, 127.70, 126.13, 113.95, 74.99, 73.03, 61.68, 53.39, 49.89, 40.95, 38.79, 36.50, 27.01, 24.02, 19.15, 17.61, 12.47; HRMS calcd for $C_{22}H_{30}O_2$ [MH^+], 327.2324; found, 327.2326.

Analog 3e. Enantiomerically pure phosphine oxide (−)-**8** and C,D-ring ketone **7e** were separately azeotropically dried with anhydrous benzene (4 × 5 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 an Ar balloon was charged with phosphine oxide (−)-**8** (35 mg, 0.06 mmol). The reagent was dissolved in 2.0 mL of freshly distilled THF and cooled to −78 °C. To this solution *n*-BuLi (38 μL, 0.06 mmol, 1.60 M solution in hexanes) was added 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 flask containing C,D-ring ketone **7e** (7 mg, 0.021 mmol) was dissolved in 0.75 mL of freshly distilled THF and cooled to −78 °C. The solution of C,D-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 4 h. Upon observation of a light yellow color, the reaction was quenched with 5 mL of pH 7 buffer and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (5% ethyl acetate in hexanes with 1% NEt_3), affording 12 mg of product. The protected analog was dissolved in THF (2 mL) and TBAF (1.0 M in THF, 150 μL) was added. After stirring overnight, the reaction was quenched with H_2O, extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (50−75% ethyl acetate in hexanes with 1% NEt_3) to afford 6.3 mg of analog **3e** as an oil (64% yield for two steps). $[\alpha]_D^{25}$ +29.2 (*c* 0.30, $CHCl_3$); IR (neat, cm^{-1}) 3346 (brs), 2925 (w), 2847 (w), 1057 (w), 906 (w), 702 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 2H), 7.29 (m, 3H), 6.37 (d, 1H, J = 11.2 Hz), 6.01 (d, 1H, J = 11.2 Hz), 5.51 (m, 1H), 5.33 (m, 2H), 5.00 (m, 1H), 4.34 (m, 4H), 3.44 (dd, 1H, J = 8.8, 3.2 Hz), 3.20 (dd, 1H, J = 8.8, 7.2 Hz), 2.81 (m, 1H), 2.59 (m, 1H), 2.31 (m, 1H), 2.05−1.26 (m, 12 H), 1.02 (d, 3H, J = 7.6 Hz), 0.86 (m, 4H), 0.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.67, 144.70, 143.09, 138.97, 132.92, 128.24, 127.66, 126.14, 124.98, 117.05, 113.84, 111.75, 75.35, 72.98, 70.84, 66.86, 56.06, 53.32, 45.99, 45.28, 42.89, 40.30, 37.13, 29.07, 27.16, 23.55, 22.35, 17.66, 12.02; HRMS calcd for $C_{31}H_{42}O_3$ [M^+], 462.3134; found, 462.3137; UV (MeOH) λ_{max} 263 nm (ϵ 14 702).

C-8 Alcohol 6f. To ice-cooled hexanes-washed NaH (9 mg of a 60% suspension in mineral oil, 0.23 mmol) was added a solution of **4** (50 mg, 0.15 mmol) in DMF (2 mL). The mixture was stirred at rt for 45 min until a light yellow color developed. Benzyl bromide (27 μL, 0.23 mmol) was added to the reaction flask and the mixture was stirred at rt for 14 h. The reaction was quenched by addition of water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (5% ethyl acetate in hexanes) to afford 53 mg of crude TES-protected alcohol. The crude TES-protected alcohol was dissolved in THF (2 mL) and TBAF (0.5 mL of a 1M solution in THF) was added. The solution was stirred overnight before being quenched with water. The mixture was extracted with dichloromethane (3 × 5 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography afforded (15% EtOAc in hexanes) 23 mg of alcohol **6f** as a colorless oil in 51% yield. $[\alpha]_D^{26}$ +34.1 (*c* 1.15, $CHCl_3$); IR (neat, cm^{-1}) 2937 (s), 2864 (s), 2357 (s), 2337 (s), 1445 (m), 1362 (w), 1163 (w), 1096 (s), 1067 (m), 1026 (w), 991 (w), 944 (w), 728 (m), 690 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.26 (m, 5H), 4.49 (q, 2H, J = 12.4 Hz), 4.08 (q, 1H, 2.4 Hz), 3.43 (dd, 1H, J = 8.8, 3.2 Hz), 3.20 (dd, 1H, J = 8.8, 7.2 Hz), 2.00 (m, 1H), 1.84−1.16 (m, 13H), 1.06 (d, 3H, J = 6.8 Hz), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.86, 128.27, 127.49, 127.37, 75.52, 73.04, 69.28, 53.45, 52.35, 41.92, 40.21, 36.36, 33.60, 26.69, 22.59, 17.45, 17.40, 13.56; HRMS calcd for $C_{20}H_{30}O_2$ [$M - H^+$], 301.2168; found, 301.2163.

C-8 Ketone 7f. A solution of alcohol **6f** (23 mg, 0.076 mmol) in CH_2Cl_2 (2 mL) was cannulated into a reaction vessel equipped with PDC (82 mg, 0.22 mmol) and oven-dried Celite (80 mg). After stirring overnight, the mixture was filtered and the filtrate was concentrated in vacuo and purified by column chromatography (10−25% ethyl acetate in hexanes) to afford 19 mg of **20** as a colorless oil in 84% yield. $[\alpha]_D^{26}$ +4.1 (*c* 0.95, $CHCl_3$); IR (neat, cm^{-1}) 2966 (s), 2884 (m), 1712 (s), 1493 (w), 1452 (w), 1395 (w), 1354 (w), 1305 (w), 1240 (w), 1216 (w), 1102 (m), 947 (w), 727 (w), 703 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.26 (m, 5H), 4.49 (q, 2H, J = 12.4 Hz), 3.43 (dd, 1H, J = 8.8, 3.2 Hz), 3.24 (dd, 1H, J = 8.8, 6.8 Hz), 2.45 (dd, 1H, J = 11.4, 7.4 Hz), 2.24 (m, 2H), 2.12 (m, 1H), 2.02−1.22 (m, 9H), 1.11 (d, 3H, J = 6.4 Hz), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.85, 138.68, 128.29, 127.49, 127.44, 75.24, 73.11, 61.66, 53.41, 49.89, 40.94, 38.79, 36.53, 27.01, 24.01, 19.14, 17.65, 12.48; HRMS calcd for $C_{20}H_{28}O_2$ [MH^+], 301.2168; found, 301.2165.

Analog 3f. Enatiomerically pure phosphine oxide (−)-**8** and C,D-ring ketone **7f** were separately azeotropically dried with anhydrous benzene (4 × 5 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 an Ar balloon was charged with phosphine oxide (−)-**8** (70 mg, 0.12 mmol). The reagent was dissolved in 2.0 mL of freshly distilled THF and cooled to −78 °C. To this solution *n*-BuLi (75 μL, 0.12 mmol, 1.60 M solution in hexanes) was added 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 flask containing C,D-ring ketone **7f** (19.0 mg, 0.063 mmol) was dissolved in 0.75 mL of freshly distilled THF and cooled to −78 °C. The solution of C,D-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 2 h. Upon observation of a light yellow color, the reaction was quenched with 5 mL of pH 7 buffer and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (5% ethyl acetate in hexanes with 1% NEt_3), affording 30.0 mg of product in a 76% yield. The protected analog was dissolved in THF (2 mL) and TBAF (1.6 M in THF, 226 μL) was added. After stirring overnight, the reaction was quenched with H_2O, extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (100% ethyl acetate with 1% NEt_3) to afford 16 mg of analog **3f** as an oil (84% yield). $[\alpha]_D^{23}$ +41.6 (*c* 0.20, $CHCl_3$); IR (neat, cm^{-1}) 3401 (m), 2944 (s), 2876 (m), 2853 (m), 1498 (w), 1445 (w), 1353 (w), 1209 (w), 1094 (m), 1049 (s), 1034 (m), 957 (w), 912 (w), 889 (w), 790 (w), 744 (s), 729 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37−7.25 (m, 5H), 6.38 (d, 1H, J = 11.2 Hz), 6.02 (d, 1H, J = 11.2 Hz), 5.32 (t, 1H, J = 1.6 Hz), 5.00 (m, 1H), 4.49 (q, 2H, J = 14 Hz), 4.43 (m, 1H), 4.23 (m, 1H), 3.44 (dd, 1H, J = 8.8 Hz, 3.2 Hz), 3.20 (dd, 1H, 8.8 Hz, 7.2 Hz) 2.83 (dd, 1H, J = 12 Hz, 3.6 Hz), 2.59 (dd, 1H, J = 13.6 Hz, 3.6 Hz), 2.31 (m, 1H), 2.05−1.24 (m, 16H), 1.10 (d, 3H, J = 6.8 Hz), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.64, 143.03, 128.83, 132.94, 128.28,

127.50, 127.38, 124.94, 117.05, 111.74, 77.20, 75.56, 73.04, 70.80, 66.83, 56.05, 53.33, 45.99, 45.25, 42.85, 40.29, 37.17, 29.06, 27.16, 23.54, 22.35, 17.69,12.03; HRMS calcd for $C_{29}H_{40}O_3$ [MH^+], 436.2978; found, 436.2980. UV (MeOH) λ_{max} 264 nm (ϵ 17 552).

C-8 Alcohol 6g. A reaction vessel charged with C-22 iodide[16] (26 mg, 0.06 mmol), freshly ground KOH (11 mg, 0.18 mmol), tetrabutylammonium hydrogen sulfate (4 mg), and furfuryl alcohol (300 μL, 3.46 mmol) was irradiated for 10 min at 175 °C. The mixture was diluted with CH_2Cl_2 (10 mL), filtered, and concentrated in vacuo. Column chromatography (5% EtOAc in hexanes) afforded 23 mg of crude TES-protected alcohol in quantitative alcohol. The crude TES-protected alcohol was dissolved in THF (2 mL) and TBAF (0.18 mL of a 1 M solution in THF) was added. The solution was stirred overnight before being quenched with water. The mixture was extracted with dichloromethane (3 × 5 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (15% EtOAc in hexanes) afforded 14 mg of alcohol **6g** as a colorless oil in 82% yield. $[\alpha]_D^{22}$ + 34.6 (*c* 0.65, $CHCl_3$); IR (neat, cm^{-1}) 3440 (br), 2906 (s), 2801 (m), 2780 (m), 1450 (w), 1283 (w), 1185 (m), 1150 (m), 1067 (m), 1015 (w), 991 (w), 944 (w), 920 (w), 886 (w), 858 (w), 812 (w), 751 (w), 697 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 1H), 6.33 (m, 1H), 6.29 (m, 1H), 4.41 (q, 2H, J = 12.8 Hz), 4.07 (m, 1H), 3.42 (dd, 1H, J = 8.8, 3.2 Hz), 3.16 (dd, 1H, J = 8.8, 7.6 Hz), 1.99 (m, 1H), 1.82−1.11 (m, 13H), 1.00 (d, 3H, J = 6.8 Hz), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.25, 142.53, 110. 15, 108.86, 75.26, 69.28, 64.91, 53.37, 52.30, 41.90, 40.16, 36.19, 33.57, 26.58, 22.57, 17.38, 17.30, 13.54; HRMS calcd for $C_{18}H_{28}O_3$ [M^+], 292.2038; found, 292.2026.

C-8 Ketone 7g. A solution of alcohol **6g** (13 mg, 0.045 mmol) in CH_2Cl_2 (5 mL) was cannulated into a reaction vessel equipped with PDC (49 mg, 0.13 mmol) and oven-dried Celite (50 mg). After stirring overnight the mixture was filtered and the filtrate was concentrated in vacuo and purified by column chromatography (10−25% ethyl acetate in hexanes) to afford 11 mg of **7g** as a colorless oil in 88% yield. $[\alpha]_D^{22}$ +4.09 (*c* 0.50, $CHCl_3$); IR (neat, cm^{-1}) 2960 (m), 2874 (m), 2850 (m), 1711 (s), 1501 (w), 1456 (w), 1380 (w), 1354 (w), 1306 (w), 1220 (w), 1150 (w), 1091 (w), 1053 (w), 1014 (w), 920 (w), 884 (w), 812 (w), 752 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 1H), 6.34 (m, 1H), 6.29 (m, 1H), 4.41 (q, 2H, J = 13.2 Hz), 3.41 (dd, 1H, J = 8.8, 3.2 Hz), 3.22 (dd, 1H, J = 8.8, 6.8 Hz), 2.44 (m, 1H), 2.31−1.29 (m, 12 H), 1.05 (d, J = 6.4 Hz), 0.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.94, 152.09, 142.61, 110.18, 109.00, 74.96, 64.95, 61.65, 53.34, 49.90, 40.95, 38.76, 36.38, 26.91, 24.02, 19.14, 17.52, 12.49; HRMS calcd for $C_{18}H_{26}O_3$ [MH^+], 291.1960; found, 291.1959.

Analog 3g. Enatiomerically pure phosphine oxide (−)-**8** and C,D-ring ketone **7g** were separately azeotropically dried with anhydrous benzene (4 × 5 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 an Ar balloon was charged with phosphine oxide (−)-**8** (45 mg, 0.077 mmol). The reagent was dissolved in 2.0 mL of freshly distilled THF and cooled to −78 °C. To this solution *n*-BuLi (50 μL, 0.08 mmol, 1.60 M solution in hexanes) was added 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 flask containing C,D-ring ketone **7g** (11 mg, 0.038 mmol) was dissolved in 0.75 mL of freshly distilled THF and cooled to −78 °C. The solution of C,D-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 6.5 h. Upon observation of a light yellow color, the reaction was quenched with 5 mL of pH 7 buffer and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give crude product that was purified by column chromatography (5% ethyl acetate in hexanes with 1% NEt_3), affording 10 mg of product in a 13% yield. The protected analog was dissolved in THF (2 mL) and TBAF (1.6 M in THF, 100 μL) was added. After stirring overnight, the reaction was quenched with H_2O, extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (50−75% ethyl acetate in hexanes with 1% NEt_3) to afford 4.5 mg of analog **3g** as an oil (70% yield). $[\alpha]_D^{23}$ +28.0 (*c* 0.20, $CHCl_3$); IR (neat, cm^{-1}) 3371 (brs), 2964 (s), 2923 (s), 2850 (m), 1667 (w), 1603 (w), 1503 (w), 1469 (w), 1434 (w), 1353 (w), 1261(w), 1218 (w), 1095 (w), 1054 (m), 1014 (w), 956 (w), 920 (w), 891 (w), 864 (w), 801 (w), 756 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (m, 1H), 6.37 (d, 1H, J = 11.2 Hz), 6.33 (m, 1H), 6.29 (m, 1H), 6.01 (d, 1H, J = 11.2 Hz), 5.32 (m, 1H), 4.99 (m, 1H), 4.42 (m, 3H), 4.23 (m, 1H), 3.44 (dd, 1H, J = 8.8, 3.2 Hz), 3.17 (dd, 1H, J = 8.8, 7.6 Hz), 2.81 (dd, 1H, J = 11.6, 3.2 Hz), 2.59 (dd, 1H, J = 13.6, 3.2 Hz), 2.31 (m, 1H), 2.08−1.20 (m, 17 H), 1.04 (d, 3H, J = 7.6 Hz), 0.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.24, 147.62, 143.07, 142.56, 132.91, 124.97, 117.77, 110.16, 109.89, 75.32, 70.82, 66.85, 64.93, 56.02, 53.26, 45.99, 45.25, 42.84, 40.26, 37.01, 29.06, 27.07, 23.54, 22.34, 17.55, 12.02; HRMS calcd for $C_{27}H_{38}O_4$ [M^+], sent in. UV (MeOH) λ_{max} 265 nm (ϵ 10 401).

C-8 Alcohol 6h. To ice-cooled hexanes-washed KH (59 mg of a 30% suspension in mineral oil, 0.44 mmol) was added a solution of **4** (17 mg, 0.05 mmol) in THF (2.5 mL). The mixture was stirred at rt for 45 min until a light yellow color developed. Tosylate **5h**[31] (70 mg, 0.26 mmol) was added to the reaction flask and the mixture was stirred at rt for 14 h. The reaction was quenched by addition of water and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (5% ethyl acetate in hexanes) to afford 20 mg of crude TES-protected alcohol. The crude TES-protected alcohol was dissolved in THF (2 mL) and TBAF (0.10 mL of a 1 M solution in THF) was added. The solution was stirred overnight before being quenched with water. The mixture was extracted with dichloromethane (3 × 5 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Column chromatography (15% EtOAc in hexanes) afforded 10 mg of alcohol **6h** as a colorless oil in 50% yield for the two steps. $[\alpha]_D^{25}$ +27.3 (*c* 0.75, $CHCl_3$); IR (neat, cm^{-1}) 3466 (br), 2966 (s), 2933 (s), 2700 (m), 2242 (w), 1658 (w), 1475 (w), 1450 (w), 1367 (w), 1259 (w), 1209 (w), 1092 (m), 992 (w), 942 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ; 4.09 (m, 3H), 3.45 (dd, 1H, J = 8.8, 3.2 Hz), 3.24 (dd, 1H, J = 8.8, 6.8 Hz), 1.99 (m, 1H), 1.92−1.03 (m, 22 H), 1.02 (d, 3H, J = 6.8 Hz), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 94.84, 74.80, 74.68, 69.32, 58.62, 53.35, 52.37, 41.88, 40.18, 36.07, 33.61, 30.98, 27.42, 26.63, 22.56, 17.45, 17.41, 13.56; HRMS calcd for $C_{20}H_{34}O_2$ [$M - H^+$], 305.2481; found, 305.2481.

C-8 Ketone 7h. A solution of alcohol **6h** (8 mg, 0.033 mmol) in CH_2Cl_2 (2 mL) was cannulated into a reaction vessel equipped with PDC (49 mg, 0.13 mmol) and oven-dried Celite (45 mg). After stirring overnight, the mixture was filtered and the filtrate was concentrated in vacuo and purified by column chromatography (10−25% ethyl acetate in hexanes) to afford 6 mg of **7h** as a colorless oil in 75% yield. $[\alpha]_D^{25}$ +1.22 (*c* 0.50, $CHCl_3$); IR (neat, cm^{-1}) 2968 (s), 2929 (s), 2849 (m), 1714 (s), 1476 (w), 1456 (m), 1381 (m), 1358 (m), 1306 (w), 1264 (m), 1239 (w), 1096 (s), 1010 (w), 942 (w), 834 (w); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.09 (m, 2H), 3.43 (dd, 1H, J = 8.8, 2.8 Hz), 3.29 (dd, 1H, J = 8.8, 6.4 Hz), 2.45 (dd, 1H, J = 11.6, 7.6 Hz), 2.28−1.28 (m, 11H), 1.22 (s, 9H), 1.07 (d, 3H, J = 6.4 Hz)m, 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.88, 94.98, 74.62, 74.36, 61.68, 58.66, 53.30, 49.85, 40.94, 38.75, 36.24, 30.94, 29.67, 26.94, 24.02, 19.09, 17.65, 12.47; HRMS calcd for $C_{20}H_{32}O_2$ [MH^+], 305.2481; found, 305.2478.

Analog 3h. Enatiomerically pure phosphine oxide (−)-**8** and C,D-ring ketone **7h** were separately azeotropically dried with anhydrous benzene (4 × 5 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 an Ar balloon was charged with phosphine oxide (−)-**8**

(35 mg, 0.06 mmol). The reagent was dissolved in 2.0 mL of freshly distilled THF and cooled to −78 °C. To this solution *n*-BuLi (34 μL, 0.054 mmol, 1.60 M solution in hexanes) was added 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 flask containing C,D-ring ketone **7h** (6 mg, 0.02 mmol) was dissolved in 0.75 mL of freshly distilled THF and cooled to −78 °C. The solution of C,D-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 5.5 h. Upon observation of a light yellow color, the reaction was quenched with 5 mL of pH 7 buffer and allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give crude product that was purified by column chromatography (5% ethyl acetate in hexanes with 1% NEt_3), affording 11 mg of product in a 84% yield. The protected analog was dissolved in THF (2 mL) and TBAF (1.6 M in THF, 100 μL) was added. After stirring overnight, the reaction was quenched with H_2O and extracted with CH_2Cl_2 (3 × 5 mL), dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo to give the crude product that was purified by column chromatography (50−75% ethyl acetate in hexanes with 1% NEt_3) to afford 4.5 mg of analog **3h** as an oil (75% yield). $[\alpha]_D^{23}$ +26.3 (*c* 0.175, $CHCl_3$); IR (neat, cm^{-1}) 3353 (br), 2970 (m), 2848 (m), 2364 (w), 1673 (w), 1465 (w), 1360 (w), 1263 (w), 1209 (w), 1095 (m), 1050 (m), 958 (w), 920 (w), 800 (w), 756 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.38 (d, 1H, *J* = 11.2 Hz), 6.02 (d, 1H, *J* = 11.2 Hz), 5.34 (m, 1H), 5.00 (m, 1H), 4.43 (m, 1H), 4.23 (m, 1H), 4.09 (m, 2H), 3.46 (dd, 1H, *J* = 8.8, 2.8 Hz), 3.25 (dd, 1H, *J* = 8.8, 7.6 Hz), 2.82 (dd, 1H, *J* = 11.6, 3.2 Hz), 2.60 (dd, 1H, *J* = 13.2, 3.6 Hz), 2.31 (m, 1H), 2.08−1.22 (m, 23H), 1.05 (d, 3H, *J* = 6.8 Hz), 0.85 (m, 2H), 0.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.65, 143.10, 132.91, 124.98, 117.04, 111.76, 94.88, 74.78, 74.69, 70.84, 66.85, 58.61, 56.07, 53.23, 45.95, 45.27, 42.87, 40.26, 36.86, 30.97, 30.31, 29.07, 27.11, 23.55, 22.32, 17.71, 12.03; HRMS calcd for $C_{29}H_{44}O_3$ [M^+], 440.3291; found, 440.3283. UV (MeOH) λ_{max} 264 nm (ε 14 229).

Gene Regulation In Vivo. C57BL/6 female mice (three mice per group) were injected i.p. with vehicle (0.1 mL PBS), compound **1** (calcitriol, 3 μg/kg), analog **3a** (25 μg/kg), or analog **3d** (25 μg/kg). Four hours later, the mice were sacrificed and duodenal mucosa was collected. Total RNA was extracted by using Tri-reagent, and semiquantitative RT-PCR was performed to detect induction of CYP24 and upregulation of the calcium channel TRPV6, using expression of GAPDH as a control.[32] The PCR products were analyzed by polyacrylamide gel electrophoresis and visualized by ethidium bromide staining of the gels.

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Supporting Information Available: ^1H and ^{13}C spectra as well as HPLC traces for compounds **3a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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