1α,25-Dihydroxyvitamin D_3 Analogs Featuring Aromatic and Heteroaromatic Rings: Design, Synthesis, and Preliminary Biological Testing

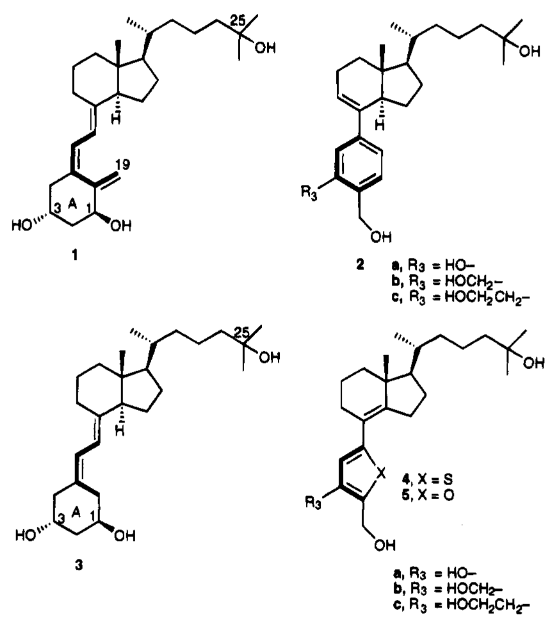
Gary H. Posner,*,† Zhengong Li,† M. Christina White,† Victoria Vinader,†,‡ Kazuhiro Takeuchi,§ Sandra E. Guggino,§,∥ Patrick Dolan,⊥ and Thomas W. Kensler⊥

Department of Chemistry, School of Arts and Sciences, The Johns Hopkins University, Baltimore, Maryland 21218, and Departments of Medicine and Neuroscience, School of Medicine, and Division of Toxicological Sciences and the Environmental Health Sciences Center, Department of Environmental Health Sciences, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Maryland 21205

Received July 27, 1995[⊗]

Aromatic compounds **2a–c**, analogs of 1α,25-dihydroxyvitamin (calcitriol, **1**), and heteroaromatic compounds **4a–c** and **5a–c**, analogs of 19-nor-1α,25-dihydroxyvitamin D_3 (**3**), were designed to simulate the topology of their biologically potent parent compounds while avoiding previtamin D equilibrium. Convergent and facile total syntheses of the analogs (+)-**2b**, (+)-**2c**, (−)-**4b**, and (−)-**5b** were achieved via carbonyl addition of regiospecifically formed organolithium nucleophiles to the enantiomerically pure C,D-ring ketone (+)-**17**, characteristic of natural calcitriol (**1**). Likewise, hybrid analogs **20a–c** were prepared to determine whether incorporation of a known potentiating side chain would lead to increased biological activity. Preliminary *in vitro* biological testing showed that aromatic analogs (+)-**2b**, (+)-**2c**, and **20a–c** as well as heteroaromatic analogs (−)-**4b** and (−)-**5b** have very low affinities for the calf thymus vitamin D receptor but considerable antiproliferative activities in murine keratinocytes at micromolar concentration. No biological advantage was observed in this keratinocyte assay for the doubly modified hybrid analogs **20a–c** over the singly modified parent (+)-**2b**. Analog (+)-**2b**, but surprisingly not the corresponding analog **20b** differing from (+)-**2b** only in the side chain, showed considerable activity in nongenomic opening of calcium channels in rat osteosarcoma cells.

Replacing a portion of the steroid skeleton with one or more aromatic rings sometimes produces potent analogs having practical therapeutic value. For example, the polyaromatic steroidal analog tamoxifen is widely used clinically for chemotherapy of breast cancer,[1] and recently developed side chain aromatic analogs of 1α,25-dihydroxyvitamin D_3 (arocalciferols) have desirably high antiproliferative activities and low calcemic activities.[2] Examination of the structure of the hormonally active 1α,25-dihydroxyvitamin D_3 (calcitriol, **1**) suggested to us that an analog having an aromatic ring in place of the conjugated triene unit characteristic of calcitriol (**1**) would have the following desirable characteristics. (1) As shown by the four darkened bonds in structures **1** and **2**, aromatic analogs **2**, having one "extra" carbon atom, would closely approximate the topology of calcitriol (**1**). (2) The 10–12 Å distance between the 25-hydroxyl group and the pseudo 1-hydroxyl group in the side chain-extended conformation of aromatic analogs **2** would be very close to that in calcitriol (**1**). (3) Varying the R_3 substituent from hydroxy (**2a**) to hydroxymethyl (**2b**) and to hydroxyethyl (**2c**) would produce analogs structurally resembling calcitriol (**1**) more and more. (4) Aromatic analogs **2** lacking ring A would be stereochemically less complex than calcitriol (**1**). (5) Incorporation of the four darkened bonds into an aromatic ring would avoid any previtamin D equilibrum.[3] (6) Aromatic analogs **2** would



be much easier to synthesize than calcitriol (**1**). Examination also of the structure of 19-norcalcitriol (**3**), an analog reported to have therapeutically valuable separation of antiproliferative activity from calcemic activity,[4] suggested that heteroaromatic analogs like **4** and **5** would have the same desirable characteristics as described above for aromatic analogs **2**. We describe here syntheses of several of these aromatic and heteroaromatic analogs and some preliminary results of their biological testing.

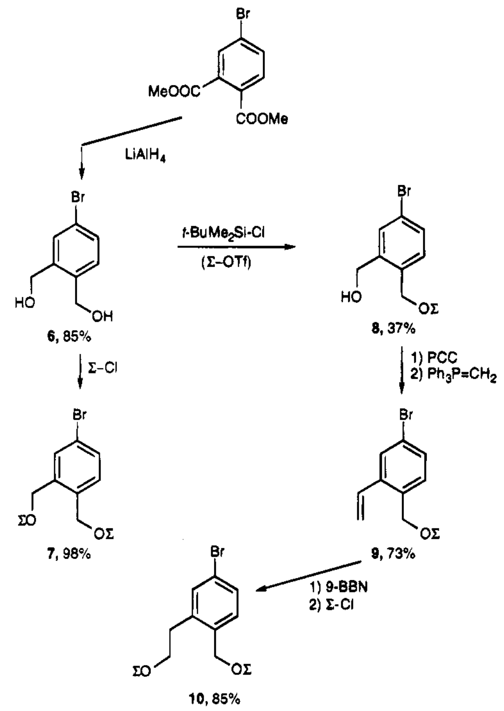
Results and Discussion

Syntheses of two aromatic analogs and of two heteroaromatic analogs were undertaken to explore the

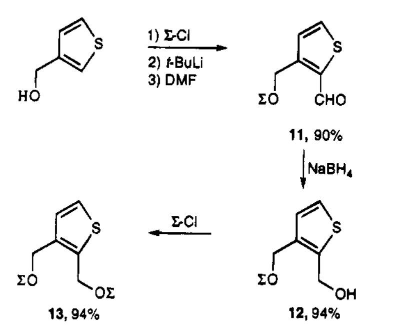
† Department of Chemistry.
‡ Current address: Glaxo Group Research Ltd., Hertfordshire, England.
§ Department of Medicine.
∥ Department of Neuroscience.
⊥ Department of Environmental Health Sciences.
⊗ Abstract published in *Advance ACS Abstracts*, October 15, 1995.

0022-2623/95/1838-4529$09.00/0

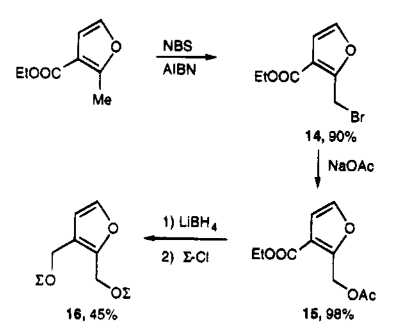
Scheme 1



Scheme 2



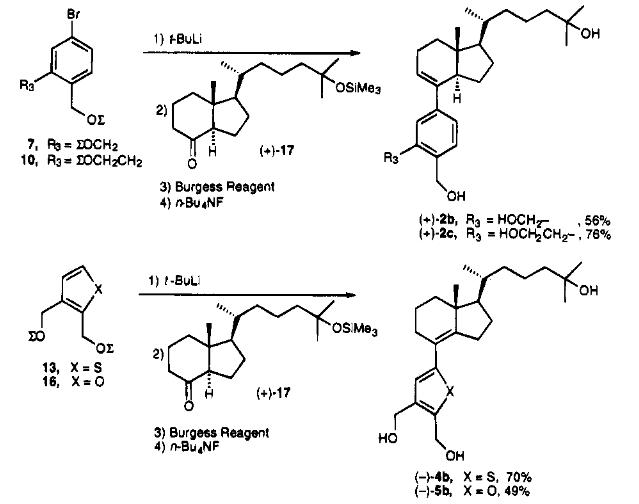
Scheme 3



chemical feasibility of this plan and to determine whether these structurally modified calcitriol analogs have any interesting biological activity. Aromatic building units **7** and **10** were prepared by bromination and esterification of phthalic acid[5] followed by the transformations shown in Scheme 1. Heteroaromatic building units **13** and **16** were prepared from commercial reactants as outlined in Schemes 2 and 3.

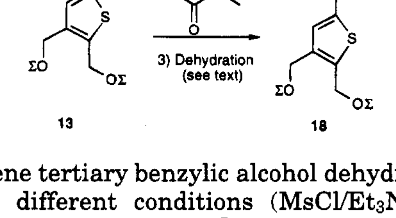
Coupling of these units to the enantiomerically pure C,D-ring unit (+)-**17**,[6] characteristic of natural calcitriol (**1**), was achieved by generation of the corresponding organolithium species that added to the ketone carbonyl group of C,D-ring ketone (+)-**17** to form the corresponding tertiary alcohols; subsequent very mild dehydration

Scheme 4



using the Burgess reagent ($CH_3O_2CN^-SO_2NEt_3^+$)[7] followed by fluoride-induced desilylation gave the four desired analogs (+)-**2b**, (+)-**2c**, (−)-**4b**, and (−)-**5b**, each in enantiomerically pure form (Scheme 4). Heteroaromatic analogs (−)-**4b** and (−)-**5b** slowly became discolored upon neat storage at 0 °C for several days; in contrast, aromatic analogs **2** were stable even at room temperature.

Noteworthy aspects of this convergent coupling process for the aromatic analogs (+)-**2b** and (+)-**2c** are as follows: (1) bromine → lithium exchange[8] allows smooth and regiospecific generation of the desired nucleophilic organolithium species and (2) dehydration of the benzylic tertiary alcohols leads exclusively to the less substituted (Hofmann)[9] olefinic products **2**, maintaining the natural *trans* stereochemistry of the C,D-ring junction. Noteworthy features of this convergent coupling process for the heteroaromatic (−)-**4b** and (−)-**5b** are as follows: (1) mild and regiospecific heteroatom-directed *ortho* lithiation[10] generates the desired nucleophilic heteroaryllithium species and (2) dehydration of the tertiary alcohol intermediates leads exclusively to the more substituted (Zaitsev)[9] alkenes (−)-**4b** and (−)-**5b**. To explore these tertiary alcohol dehydration reactions that lead, with the same Burgess reagent, to the aromatic more substituted alkene products **2b** and **2c** but to the heteroaromatic less substituted alkene products **4b** and **5b**, the model dehydrations shown in eq 1 were examined. In this structurally simpler case, the



(1)

thiophene tertiary benzylic alcohol dehydrations under several different conditions (MsCl/Et_3N, Al_2O_3/benzene,[11] or Burgess reagent[7]) now lead exclusively to the less substituted alkene **18**; attempts to dehydrate this thiophene tertiary benzylic alcohol or the corresponding furan tertiary benzylic alcohol using a catalytic amount of *p*-toluenesulfonic acid in benzene at reflux for 30 min resulted in substrate decomposition, as expected for carbocations formed via acid-promoted ionization of

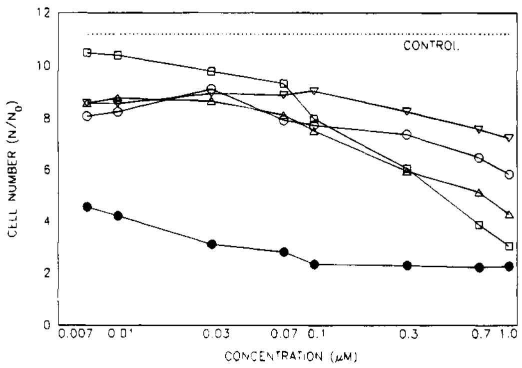


Figure 1. Dose response effects of deltanoids on keratinocyte proliferation (96 h).

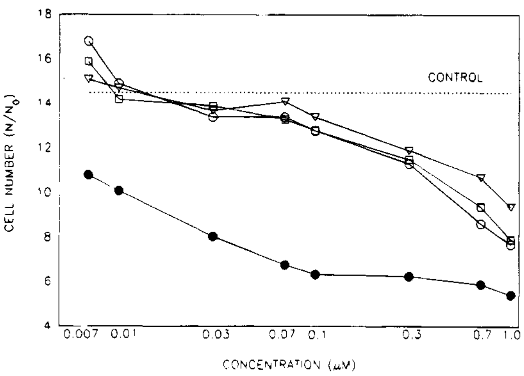


Figure 2. Dose response of PE cells exposed to D_3 analogs (96 h growth curve).

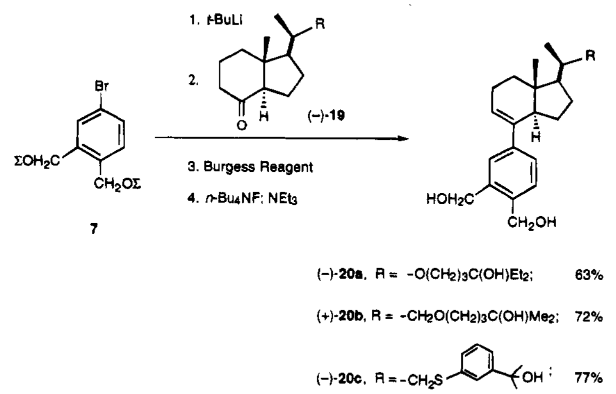
hydroxymethyl furans and thiophenes.[12] The exclusive formation in the thiophene series of the less substituted alkene in eq 1 vs the more substituted alkene **4b** in Scheme 4 emphasizes the fact that subtle and as yet not clearly understood aspects of these dehydration reactions are important.[9]

Preliminary *in vitro* biological testing of these calcitriol analogs **2**, **4**, and **5** in murine keratinocytes, according to our previous protocol,[13] gave the results shown in Figure 1.

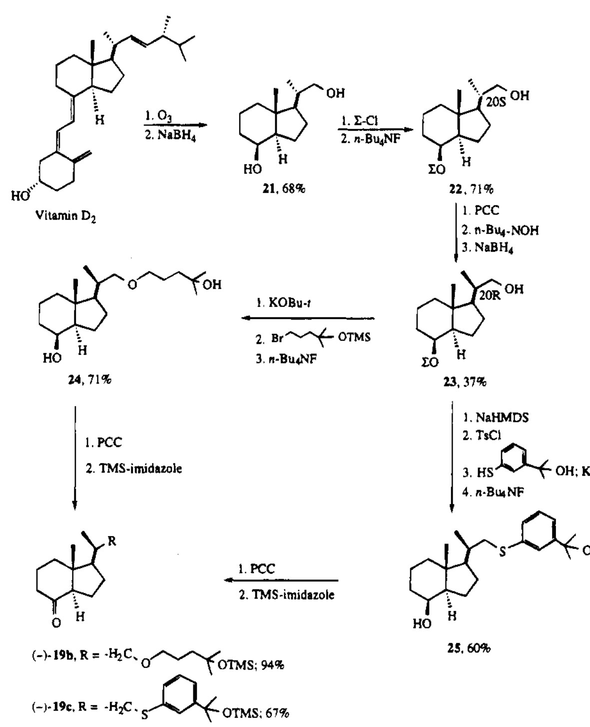
Several conclusions emerge from these antiproliferative results. (1) At 1.0 μM concentrations, all four analogs show measurable antiproliferative activity. (2) At this concentration, both aromatic analogs (+)-**2** are at least as active as heteroaromatic analogs (−)-**4b** and (−)-**5b** and almost as active as natural calcitriol (**1**). (3) No advantage in antiproliferative potency is observed in going from hydroxymethyl analog (+)-**2b** to hydroxyethyl analog (+)-**2c**. (4) At 0.1 μM (100 nM) concentrations, the activities of all four analogs relative to control are not impressive. These findings indicate clearly that, despite the very substantial structural changes and stereochemical simplifications made in the design of these four analogs vs calcitriol (**1**), considerable antiproliferative activity remains, especially at 1.0 μM concentrations.

Structural modification of the side chain of calcitriol (**1**) has led, in some noteworthy cases, to vitamin D analogs having considerably enhanced biological activities. For example, combining incorporation of an extra oxygen atom at the 22- and 23-positions and incorporation of a sulfur atom at the 23-position along with inversion of stereochemistry at the 20-position has produced potent antiproliferative analogs.[14,15] Recently, we showed for the first time that combining structural

Scheme 5



Scheme 6



changes at both the C,D-ring side chain and the A-ring produces a hybrid analog having blended and powerful antiproliferative activities.[16a] Therefore, in the hope of enhancing the biological potency of easily prepared aromatic analog (+)-**2b**, we synthesized three hybrid analogs, each carrying a strongly potentiating side chain modification as shown in Scheme 5.[14–16] In these systems also, Burgess reagent dehydration led exclusively to the less substituted (Hofmann) styrene product **20**.

We have recorded preparation of the requisite C,D-ring chiron (−)-**19a** previously,[16a] and preparation of the C,D-ring chirons (−)-**19b** and (−)-**19c** from inexpensive and commercial vitamin D_2 is shown in Scheme 6.[14,15] The *in vitro* antiproliferative activities of hybrid aromatic analogs **20a–c** in murine keratinocytes are shown in Figure 2.

Similar to the results shown in Figure 1, these three analogs (−)-**20a–c** all showed considerable antiproliferative activities at 1 μM concentrations. Thus, in sharp contrast to our recent finding of a potentiating effect due to incorporation of the KH-1060 type side chain[14b] into an analog containing a 1-hydroxymethyl group,[16a,d] doubly modified hybrid analogs (−)-**20a–c** are no more

Table 1. Calcium Current Measurements

compound	calcium currents (mV)[a]		
	50.0 nM	5.0 nM	0.5 nM
1	10.17 ± 0.54	9.79 ± 0.19	5.73 ± 1.33
(+)-**2b**	7.03 ± 0.93	1.45 ± 0.38	−0.08 ± 0.69
(+)-**20b**	0.63 ± 0.32	0.15 ± 0.12	0.02 ± 0.02

[a] At various concentrations of analogs (mean ± standard error, $n = 3-5$).

potent in this assay than their singly modified parent analog (+)-**2b**. All of the seven analogs described here had, at 1−50 μM concentrations, no more than 10^{-3} the affinity of calcitriol (**1**) for the calf thymus vitamin D receptor (VDR).

Exploring the nongenomic, instantaneous opening of calcium channels in rat osteosarcoma cells by some of these analogs, using the previously described patch−clamp technique,[16b] we have found the dramatic results that aromatic analog (+)-**2b** is almost as effective as calcitriol (**1**) at 50.0 nM concentrations and that the affinity of (+)-**2b** to the nongenomic receptor is 100-fold lower than that of **1**. Despite the expectation that hybrid analog (+)-**20b**, having a potentiating side chain,[16a,d] would be even more potent than analog (+)-**2b**, having the natural calcitriol side chain, hybrid analog (+)-**20b** was found to be almost inactive at 50.0 nM concentrations (see Table 1). Thus, the nature of the C,D-ring side chain, the only structural difference between analogs (+)-**2b** and (+)-**20b**, appears to be critical in governing calcium channel opening.

In conclusion, seven new aromatic and heteroaromatic vitamin D_3 analogs have been easily prepared, with each one lacking the natural calcitriol-conjugated triene unit and also lacking calcitriol's stereochemical complexity in the A-ring. Although they all bind poorly to the calf thymus VDR even at micromolar concentrations, they all show substantial antiproliferative activities in murine keratinocytes at 1 μM concentrations. Also, even though aromatic analog (+)-**2b** lacks the conjugated triene unit and the stereochemical complexity of calcitriol (**1**), it is nearly as effective as calcitriol at 50.0 nM concentrations in gating calcium channels *in vitro*. Thus, these results show that substantial structural variations can be made to calcitriol (**1**) in the design of steroid mimetic analogs like (+)-**2b** that have selective and considerable biological activities. More thorough evaluation of the full spectrum of biological activities of these nonclassical calcitriol analogs (deltanoids)[17] will reveal whether they have any practical medicinal value. We are ready to supply small quantities of these and related new compounds having selective biological activities to those interested in testing them further.

Experimental Section

General. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone ketyl prior to use. Methylene chloride (CH_2Cl_2) and triethylamine (NEt_3) were distilled from calcium hydride prior to use. Commercially available anhydrous solvents were used in other instances. All reagents were purchased from Aldrich Chemical Co. (Milwaukee, WI) and were used as received without further purification. FT-IR and UV spectra were recorded using a Perkin-Elmer Model 1600 FT-IR spectrophotometer and a Beckman Du-70 spectrophotometer, respectively. The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. High-resolution mass spectral data were obtained using a VG-70S mass spectrometer run at 70 eV. Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA. The melting point is uncorrected. Concentrations for optical rotations were given in grams per 100 mL. Unless otherwise indicated, all reactions were run under an Ar atmosphere. The purity of products was judged to be at least 95% on the basis of their chromatographic homogeneity.

3,4-Bis(hydroxymethyl)-1-bromobenzene (6). To a stirred solution of dimethyl 4-bromophthlate (5.00 g, 18.3 mmol) in THF (25 mL) and ether (25 mL) at 0 °C was added 1.0 M LAH solution (20.3 mL, 20.3 mmol) in ether during a period of 30 min. After the addition was over, the resulting reaction mixture was stirred at room temperature for 1 h and refluxed gently for 1.5 h. The reaction mixture was quenched with water (12 mL) and concentrated HCl (12 mL) and extracted with ether. The combined organic phase was washed once with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was distilled (140 °C, 0.05 mmHg) using Kugelrohr to afford 3.36 g (15.5 mmol, 85%) of the desired diol as a white solid: mp 75.2−76.4 °C; ^1H NMR ($CDCl_3$) δ 7.44 (d, J = 2.0 Hz, 1H), 7.40 (dd, J = 8.0 and 2.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 4.55 (s, 4H), 3.71 (s, 2H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$) δ 141.18, 137.86, 132.14, 131.20, 131.03, 122.06, 63.05; IR ($CDCl_3$) 3604, 3428, 2929, 2886, 2249, 1013, 922, 911, 872, 756, 650 cm^{-1}; HRMS m/z ($M^+ - t$-Bu) calcd for $C_8H_9BrO_2$ 215.9786, found 215.9788. Anal. Calcd for $C_8H_9O_2Br$: C, 44.27; H, 4.18; Br, 36.81. Found: C, 44.24; H, 4.13; Br, 36.72.

3,4-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-bromobenzene (7). To a stirred solution of *tert*-butyldimethylsilyl chloride (TBDMSCl) (1.67 g, 11.1 mmol), 4-(dimethylamino)-pyridine (DMAP) (136 mg, 1.11 mmol) in NEt_3 (10 mL), and dimethylformamide (DMF) (15 mL) was added diol **6** (1.0 g, 4.61 mmol) in THF (5 mL). The resulting reaction mixture was stirred at room temperature for 2 h, the reaction quenched with saturated $NaHCO_3$ solution (20 mL), and the mixture diluted with ether (50 mL). The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phase was washed once with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (1% EtOAc/hexanes) to afford 2.05 g (4.61 mmol, quantitative) of the bissilylated product **7** as an oil: ^1H NMR ($CDCl_3$) δ 7.47 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.0 and 2.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 4.68 (s, 2H), 4.63 (s, 2H), 0.96 (s, 9H), 0.94 (s, 9H), 0.12 (s, 6H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.49, 136.89, 129.78, 129.28, 128.24, 121.04, 62.31, 62.06, 25.91, 18.36, −5.32; IR ($CDCl_3$) 2930, 2885, 2858, 2245, 1463, 1257, 1128, 1006, 838, 743, 716 cm^{-1}; HRMS m/z ($M^+ - t$-Bu) calcd for $C_{20}H_{37}BrO_2Si_2$ 387.0811, found 387.0812.

4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-(hydroxylmethyl)-1-bromobenzene (8). To a stirred solution of diol **6** (1.0 g, 4.61 mmol) in THF (10 mL) at room temperature was added dropwise a solution of TBDMSCl (764 mg, 5.07 mmol) and DMAP (619 mg, 5.07 mmol) in DMF (20 mL). The resulting solution was stirred at room temperature for 1 h, the reaction quenched with saturated $NaHCO_3$ (2 mL), and the mixture diluted with ether (50 mL). The organic layer was separated, and the aqueous phase was extracted with ether. The combined organic phase was washed once with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (5% EtOAc/hexanes) to afford the monosilylated product **8** (561 mg, 37%) as an oil: ^1H NMR ($CDCl_3$) δ 7.54 (d, J = 2.0 Hz, 1H), 7.41 (dd, J = 8.0 and 2.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 4.73 (s, 2H), 4.64 (d, J = 6.4 Hz, 2H), 3.01 (t, J = 6.4 Hz, 1H, D_2O exchangeable), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 141.59, 137.50, 131.88, 130.74, 130.03, 121.85, 63.84, 63.07, 25.83, 18.23, −5.26; IR ($CDCl_3$) 3428, 2980, 2931, 2860, 2244, 1046, 923, 901, 743 cm^{-1}; HRMS m/z ($M^+ - t$-Bu) calcd for $C_{14}H_{23}BrO_2Si$ 272.9946, found 272.9948.

4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-3-vinyl-1-bromobenzene (9). A mixture of **8** (189 mg, 0.57 mmol), PCC (260 mg, 1.20 mmol), and dry Celite (200 mg) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1.5 h. The reaction mixture was passed through silica gel (4 g), eluting with a 1:1 mixture of hexanes/ether (30 mL), and evaporation of solvents under reduced pressure afforded 160 mg (0.49 mmol, 85%) of the aldehyde intermediate as an oil. To a solution of methyltriphenylphosphonium bromide (347 mg, 0.97 mmol) in THF (20 mL) at 0 °C was added dropwise a 1.8 M phenyllithium solution (0.48 mL, 0.87 mmol) in cyclohexane/ether. The resulting red ylide solution was then warmed to room temperature, stirred for 3 h, and cooled to −78 °C. To this ylide solution was added via cannula the above prepared aldehyde (160 mg, 0.49 mmol) in THF (5 mL). After being stirred for 1 h at −78 °C, the reaction mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with water (2 mL) and the mixture diluted with ether (20 mL). The organic phase was separated and the aqueous phase extracted with ether. The combined organic phase was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (5% EtOAc/hexanes) to afford 137 mg (0.42 mmol, 87%) of styrene **9** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 2.0 Hz, 1H), 7.34 (dd, J = 8.0 and 2.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 6.74 (dd, J = 17.6 and 10.8 Hz, 1H), 5.63 (dd, J = 17.6 and 1.2 Hz, 1H), 5.33 (dd, J = 10.8 and 1.2 Hz, 1H), 4.70 (d, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.56, 137.04, 136.61, 130.44, 128.56, 128.28, 121.07, 117.10, 62.55, 25.89, 18.34, −5.24; IR ($CDCl_3$) 2956, 2930, 2857, 2885, 1590, 1558, 1472, 1463, 1257, 1124, 1088, 922, 752, 652 cm^{-1}; HRMS m/z (M^+ − t-Bu) calcd for $C_{15}H_{23}BrOSi$ 268.9997, found 268.9994.

3-[[(*tert*-Bultyldimethylsilyl)oxy]ethyl]-4-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1-bromobenzene (10). To a solution of styrene **9** (135 mg, 0.41 mmol) in THF (2 mL) at 0 °C was added slowly 0.5 M 9-BBN solution (1.65 mL, 0.82 mmol) in THF. After the addition, the reaction mixture was warmed to room temperature and stirred for 4 h. Ethanol (0.6 mL) was added carefully to the reaction mixture, followed by 6 N NaOH solution (0.2 mL) and 30% H_2O_2 solution (0.4 mL). The reaction mixture was then heated at 50 °C for 1 h, cooled to room temperature, and extracted with ether. The organic phase was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (10% EtOAc/hexanes) to give 126 mg (0.36 mmol, 89%) of the phenylethanol intermediate as an oil. This was then silylated by following the same procedure for preparation of **8**, and the reagents utilized were as follows: TBDMSCl (65 mg, 0.43 mmol) and DMAP (53 mg, 0.43 mmol). This afforded 159 mg (0.35 mmol, 96%) of O-silylated product **10** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.36−7.28 (m, 3H), 4.66 (s, 2H), 3,79 (t, J = 6.8 Hz, 2H), 2.79 (t, J = 6.8 Hz, 2H), 0.94 (s, 9H), 0.84 (s, 9H), 0.11 (s, 6H), −0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.54, 138.28, 132.66, 129.21, 128.69, 120.61, 63.45, 62.58, 35.22, 25.94, 25.90, 18.37, 18.30, −5.26, −5.47; IR ($CDCl_3$) 2955, 2943, 2885, 2858, 1472, 1251, 1070, 836, 778 cm^{-1}; HRMS m/z (M^+ − t-Bu) calcd for $C_{21}H_{39}BrO_2Si$ 401.0968, found 401.0969.

3-[(*tert*-Butyldimethylsilyl)oxy]-2-thiophenecarboxaldehyde (11). To a stirred solution of TBDMSCl (1.45 g, 9.64 mmol), DMAP (117 mg, 0.96 mmol) in NEt_3 (15 mL, 0.11 mol), and DMF (15 mL) at room temperature was added 3-thiophenemethanol (1.0 g, 8.8 mmol) in THF (5 mL) via syringe. The resulting reaction mixture was stirred for 1 h at room temperature and diluted with ether (50 mL) and the reaction quenched with saturated NH_4Cl solution (10 mL). The organic phase was separated, and the aqueous layer was extracted with ether. The combined organic phase was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude 3-[(*tert*-butyldimethylsilyl)oxy]thiophene as an intermediate. This was dissolved in anhydrous ether (10 mL), and the solution was cooled to −10 °C under Ar. To this was added a 1.7 M t-BuLi solution (5.2 mL, 8.8 mmol) in pentane for a period of 20 min. The resulting reaction mixture was stirred at −10 °C for 30 min, and DMF (1.0 mL, 13.7 mmol) was slowly added to the mixture. The reaction temperature was raised to 0 °C, and the reaction mixture was stirred at this temperature for 30 min. The reaction was quenched with saturated NH_4Cl solution (2 mL) and the mixture extracted with ether. The organic phase was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (2% EtOAc/hexanes) to afford 2.02 g (7.9 mmol, 90%) of the required aldehyde **11** as an oil: ^{1}H NMR δ 10.08 (s, 1H), 7.64 (d, J = 4.8 Hz, 1H), 7.20 (d, J = 4.8 Hz, 1H), 5.04 (s, 2H), 0.92 (s, 9H), 0.097 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 182.69, 151.05, 136.95, 133.98, 129.18, 60.54, 25.80, 18.23, −5.40; IR ($CDCl_3$) 2956, 2858, 1660, 1426, 1257, 1106, 897, 838, 780, 758, 747 cm^{-1}; HRMS m/z (M^+ − t-Bu) calcd for $C_{12}H_{20}O_2SSi$ 199.0249, found 199.0251.

3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2-thiophenemethanol (12). To a stirred solution of $NaBH_4$ (280 mg, 9.4 mmol) in CH_3OH (5 mL) at room temperature was added aldehyde **11** (1.72 g, 6.71 mmol) in THF (5 mL). The resulting reaction mixture was stirred for 30 min at room temperature, the reaction quenched with saturated NH_4Cl solution (10 mL) carefully, and the mixture extracted with ether. The combined organic phase was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (10% EtOAc/hexanes) to give 1.63 g (6.28 mmol, 94%) of the desired thiophenemethanol as an oil: ^{1}H NMR δ 7.13 (d, J = 5.2 Hz, 1H), 6.94 (d, J = 5.2 Hz, 1H), 4.74 (s, 2H), 4.71 (s, 2H), 3.32 (br s, 1H, D_2O exchangeable), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 139.30, 138.44, 128.24, 123.22, 59.80, 57.47, 25.80, 18.22, −5.40; IR (neat) 3382, 2928, 2856, 1471, 1254, 1075, 835, 775 cm^{-1}; HRMS m/z (M^+ − t-Bu) calcd for $C_{12}H_{22}O_2SSi$ 201.0406, found 201.0407.

2,3-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]thiophene (13). This was prepared from **12** by following the same procedure described for **8**. The reagents used were as follows: 2-thiophenemethanol **12** (1.60 g, 6.19 mmol), TBDMSCl (1.12 g, 7.43 mmol), DMAP (90 mg, 0.74 mmol), and NEt_3 (5 mL). This afforded 2.17 g (5.82 mmol, quantitative) of the O-silylated thiophene **13** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.12 (d, J = 5.2 Hz, 1H), 6.95 (d, J = 5.2 Hz, 1H), 4.86 (s, 2H), 4.67 (s, 2H), 0.93 (s, 9H), 0.91 (s, 9H), 0.10 (s, 6H), 0.073 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 139.93, 136.69, 127.87, 122.74, 59.61, 59.22, 25.92, 25.86, 18.35, −5.31, −5.33; IR ($CDCl_3$) 2930, 2885, 2857, 1472, 1464, 1075, 838, 779 cm^{-1}; HRMS m/z (M^+ − t-Bu) calcd for $C_{18}H_{36}O_2SSi_2$ 315.1270, found 315.1266.

Ethyl 2-(Bromomethyl)-3-furoate (14). To an NBS (1.75 g, 9.73 mmol) suspension in anhydrous CCl_4 (50 mL) was added ca. 0.1 g of AIBN while the suspension was gently refluxed. After 30 s, ethyl 2-methyl-3-furoate (1.50 g, 9.73 mmol) was added via syringe; the resulting reaction mixture was refluxed for 20 min, cooled to room temperature, and then cooled in an ice bath. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (10% EtOAc/hexanes) to afford 2.04 g (8.75 mmol, 90%) of the brominated product **14** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.37 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 4.80 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.67, 155.16, 142.60, 116.13, 111.38, 60.73, 21.21, 14.21; IR (neat) 2984, 1717, 1605, 1508, 1430, 1305, 1262, 1196, 1138, 1097, 1048, 750 cm^{-1}; HRMS m/z (M^+) calcd for $C_8H_9BrO_3$ 231.9735, found 231.9739.

Ethyl 2-(Acetoxymethyl)-3-furoate (15). A mixture of **14** (1.05 g, 4.50 mmol), NaOAc (660 mg, 8.0 mmol) in CH_3CN (20 mL), and DMF (10 mL) was refluxed for 3 h. The reaction mixture was diluted with ether (50 mL) and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was distilled (90 °C, 0.1 mmHg) to give 935 mg (441 mmol, 98%) of the desired product as an oil: ^{1}H NMR ($CDCl_3$) δ 7.37 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 5.37 (s, 2H), 4.29 (q, J = 7.2 Hz, 2H), 2.08 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.55, 162.77, 154.00, 142.58, 117.82, 111.05, 60.65, 56.88, 20.64, 14.18; IR (neat) 2984, 2360, 1748, 1719, 1611, 1308, 1232, 1188, 1092, 1037, 754, 603 cm^{-1}; HRMS m/z (M^+) calcd for $C_{10}H_{12}O_5$ 212.0685, found 212.0687.

2,3-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]furan (16). To the suspension of $LiBH_4$ (308 mg, 14.1 mmol) in ether (10 mL) was added dropwise ester **15** (500 mg, 2.35 mmol) in ether (5 mL). To this was added dropwise CH_3OH (0.6 mL, 14.1 mmol) for a period of 20 min, and the resulting reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature, the reaction quenched with saturated

NH_4Cl solution (15 mL) carefully, and the mixture stirred at room temperature for 1 h. The reaction mixture was extracted with EtOAc, and the combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude 2,3-furandimethanol. This was immediately dissolved in anhydrous THF (2 mL) and added via cannula to a stirred solution of TBDMSCl (440 mg, 2.92 mmol), DMAP (354 mg, 0.29 mmol) in NEt_3 (5 mL, 35.9 mmol), and DMF (2 mL). The resulting reaction mixture was stirred at room temperature for 2 h, the reaction quenched with saturated $NaHCO_3$ (2 mL), and the mixture diluted with ether (50 mL). The organic phase was separated, and the aqueous phase was extracted with ether. The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (1% EtOAc/hexanes) to afford 419 mg (1.17 mmol, 50%) of the 2,3-bissilylated furandimethanol **16** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.31 (d, J = 2.0 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 4.66 (s, 2H), 4.61 (s, 2H), 0.92 (s, 9H), 0.91 (s, 9H), 0.092 (s, 6H), 0.085 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 149.32, 141.35, 121.81, 110.94, 56.93, 56.36, 25.92, 25.89, 18.41, 18.36, −5.23, −5.30; IR ($CDCl_3$) 2956, 2930, 2885, 2858, 1472, 1464, 1149, 1064, 838, 779 cm^{-1}; HRMS m/z ($M^+ - t$-Bu) calcd for $C_{18}H_{36}O_3Si_2$ 299.1499, found 299.1500.

2,3-Bis[[(*tert*-butyldimethylsilyl)oxy]methyl]-5-(6′-methyl-1′-cyclohexenyl)thiophene (18). To a stirred solution of thiophene **12** (60 mg, 0.16 mmol) in ether (0.5 mL) at −10 °C under Ar was added dropwise a 1.7 M t-BuLi solution (0.10 mL, 0.17 mmol) in pentane. The resulting reaction mixture was stirred at −10 °C for 30 min and then cooled to −78 °C. To this was added 2-methylcyclohexanone (9 mg, 0.08 mmol) in ether (0.5 mL) via cannula. The resulting reaction mixture was stirred under −78 °C for 2 h, the reaction quenched with saturated NH_4Cl solution (0.1 mL), and the mixture extracted with ether. The organic phase was dried over $MgSO_4$, concentrated under reduced pressure, and chromatographed on silica gel (5% EtOAc/hexanes) to give 24 mg (0.05 mmol, 61%) of the tertiary alcohol as the coupling intermediate. This was immediately dissolved in anhydrous benzene (2 mL) containing Burgess reagent (36 mg, 0.15 mmol), and the reaction mixture was stirred overnight at room temperature, then refluxed for 1 h, and chromatographed on silica gel (1% EtOAc/hexanes) to afford 14 mg (0.03 mmol, 60%) of the dehydrated product **18** as an oil: ^{1}H NMR ($CDCl_3$) δ 6.78 (s, 1H), 6.00 (t, J = 4.0 Hz, 1H), 4.81 (s, 2H), 4.62 (s, 2H), 2.75−2.64 (m, 1H), 2.22−2.13 (m, 2H), 1.84−1.57 (m, 4H), 1.14 (d, J = 7.2 Hz, 3H), 0.93 (s, 9H), 0.91 (s, 9H), 0.10 (s, 6H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 143.74, 136.91, 136.76, 136.61, 123.67, 122.44, 59.65, 59.10, 30.57, 30.02, 25.92, 25.89, 20.24, 18.38, 18.35, 17.42, −5.26, −5.28; IR ($CDCl_3$) 2956, 2931, 2858, 2243, 1472, 1362, 1256, 1089, 894, 838, 779, 736, 650 cm^{-1}; HRMS m/z (M^+) calcd for $C_{25}H_{46}O_2SSi_2$ 466.2757, found 466.2762.

Aromatic Analog 2b. To a stirred solution of bromobenzene **7** (57 mg, 0.13 mmol) in THF (0.5 mL) at −78 °C under Ar was added a 1.7 M t-BuLi solution (83 μL, 0.14 mmol) in pentane, and the resulting solution was stirred at −78 °C for 30 min before C,D-ring (+)-**17** (15 mg, 0.04 mmol) in THF (1 mL) was added via cannula to the reaction mixture. The reaction mixture was stirred at −78 °C for 2 h, the reaction quenched with saturated NH_4Cl solution (0.1 mL) under the same temperature, and the mixture extracted with ether (3 × 4 mL). The organic phase was dried over $MgSO_4$, concentrated under reduced pressure, and purified by preparative TLC (silica gel 1000 μm, 10% EtOAc/hexanes) to give 19 mg (0.03 mmol, 63%) of the crude coupling product. This was immediately dissolved in anhydrous benzene (2 mL) containing Burgess reagent (19 mg, 0.08 mmol), and the reaction mixture was stirred at room temperature for 1 h, then refluxed for 2 h, and chromatographed on silica gel (1% EtOAc/hexanes) to give 17 mg (0.02 mmol, 90%) of the dehydrated product. This was dissolved in anhydrous THF (1 mL). NEt_3 (30 μL) and a 1.0 M n-Bu_4NF solution (85 μL, 0.08 mmol) in THF were added, and the resulting reaction mixture was stirred at room temperature for 12 h and purified by preparative TLC (silica gel 1000 μm, 5% MeOH/EtOAc) to afford 10 mg (0.02 mmol, 56% overall from **17**) of the title compound as a gum: ^{1}H NMR ($CDCl_3$) δ 7.24 (d, J = 7.6 Hz, 1H), 7.19 (d, J = 2.0 Hz, 1H), 7.13 (dd, J = 7.6 and 2.0 Hz, 1H), 5.67−5.61 (m, 1H), 4.70 (s, 2H), 4.69 (s, 2H), 2.64−0.83 (m, 26H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.39, 139.80, 138.88, 137.05, 129.30, 128.33, 126.79, 125.53, 71.14, 64.44, 54.36, 49.84, 44.36, 42.65, 36.38, 36.15, 35.93, 29.32, 29.16, 28.34, 25.05, 24.44, 20.81, 18.80, 11.28; IR ($CHCl_3$) 3605, 3472, 2965, 2931, 2872, 2246, 1608, 1011, 894, 756, 741, 723, 62 cm^{-1}; UV (MeOH) λ_{max} 248 nm (ϵ = 17 800); $[\alpha]^{23}{}_D$ +42.7 (c = 0.62, CH_2Cl_2); HRMS m/z (M^+) calcd for $C_{26}H_{40}O_3$ 400.2977, found 400.2980.

Aromatic Analog 2c. This was prepared by following the same procedure described for **2b**. The reagents utilized were as follows: **10** (59 mg, 0.13 mmol), t-BuLi (75 μL, 0.13 mmol, 1.7 M solution in pentane), C,D-ring (+)-**17** (15 mg, 0.04 mmol), Burgess reagent (28 mg, 0.12 mmol), and n-Bu_4NF (0.12 mL, 0.12 mmol, 1.0 M solution in THF). This afforded 13 mg (0.03 mmol, 76% overall from (+)-**17**) of the title compound as a gum: ^{1}H NMR ($CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 1H), 7.08−7.05 (m, 2H), 5.66−5.62 (m, 1H), 4.63 (s, 2H), 3.90 (t, J = 5.6 Hz, 2H), 2.94 (t, J = 5.6 Hz, 2H), 2.62−0.96 (m, 29H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.32, 139.96, 137.48, 137.08, 129.38, 128.52, 125.27, 125.23, 71.12, 63.56, 63.00, 54.36, 49.87, 44.37, 42.65, 36.40, 36.14, 35.95, 35.21, 29.31, 29.16, 28.35, 25.04, 24.48, 20.80, 18.81, 11.29; IR ($CDCl_3$) 3605, 3424, 2963, 2919, 2872, 2246, 1606, 1044, 900, 742, 648 cm^{-1}; UV (MeOH) λ_{max} 247 nm (ϵ = 16 300); $[\alpha]^{23}{}_D$ +44.3 (c = 1.12, CH_2Cl_2); HRMS m/z (M^+) calcd for $C_{27}H_{42}O_3$ 414.3134, found 414.3135.

Heteroaromatic Analog 4b. To a stirred solution of thiophene **13** (79 mg, 0.21 mmol) in anhydrous ether (0.5 mL) at −10 °C under Ar was added dropwise a 1.7 M t-BuLi solution (0.12 mL, 0.21 mmol) in pentane, and the resulting reaction mixture was stirred at −10 °C for 30 min and then cooled to −78 °C before C,D-ring (+)-**17** (25 mg, 0.07 mmol) in ether (1.0 mL) was added via cannula dropwise. After addition was over, the reaction mixture was stirred for 2 h under −78 °C, and the reaction was quenched with saturated NH_4Cl solution (0.15 mL) at the same temperature. The reaction mixture was extracted with ether (3 × 5 mL), and the combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (silica gel 1000 μm, 10% EtOAc/hexanes) to afford 48 mg (0.07 mmol, 92%) of the crude coupling product. This was then subject to dehydration and deprotection by following the same procedure described for **2b**. The reagents utilized were as follows: Burgess reagent (47 mg, 0.20 mmol) and n-Bu_4NF (0.18 mL, 0.18 mmol, 1.0 M solution in THF). This afforded 20 mg (0.05 mmol, 70% from **17**) of the title compound as a gum: ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 1H), 4.76 (s, 2H), 4.65 (s, 2H), 2.56−0.82 (m, 30H); ^{13}C NMR ($CDCl_3$) δ 147.77, 144.48, 138.59, 137.03, 125.36, 120.68, 71.14, 58.76, 57.41, 55.46, 44.68, 44.34, 36.92, 36.13, 34.40, 29.27, 29.18, 28.86, 27.48, 20.76, 19.28, 19.01, 18.60; IR ($CHCl_3$) 3605, 3442, 2361, 1371 cm^{-1}; UV (MeOH) λ_{max} 285 nm (ϵ = 19 000); $[\alpha]^{23}{}_D$ −30.9 (c = 0.10, CH_2Cl_2); HRMS m/z (M^+) calcd for $C_{24}H_{38}O_3S$ 406.2542, found 406.2546.

Heteroaromtic Analog 5b. To a stirred solution of furan **16** (73 mg, 0.20 mmol) in anhydrous ether (0.5 mL) at −40 °C under Ar was added dropwise a 1.7 M t-BuLi solution (0.12 mL, 0.20 mmol) in pentane, and the resulting reaction mixture was stirred at −40 °C for 30 min and then cooled to −78 °C before C,D-ring (+)-**17** (24 mg, 0.07 mmol) in ether (1.0 mL) was added via cannula dropwise. After addition, the reaction mixture was stirred for 2 h under −78 °C, and the reaction was quenched with saturated NH_4Cl solution (0.15 mL) at the same temperature. The reaction mixture was extracted with ether (3 × 5 mL), and the combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by preparative TLC (silica gel 1000 μm, 10% EtOAc/hexanes) to afford 42 mg (0.06 mmol, 79%) of the crude coupling product. This was then subjected to dehydration and deprotection by following the same procedure described for **2b**. The reagents utilized were as follows: Burgess reagent (38 mg, 0.16 mmol), NEt_3 (30 μL), and a 1.0 M n-Bu_4NF solution (0.16 mL, 0.16 mmol) in THF. This afforded 13 mg (0.03 mmol, 49% overall from (+)-**17**) of the title compound as a gum. This compound was unstable when stored neat at 0 °C; however, it was stable at −30 °C: ^{1}H NMR ($CDCl_3$) δ 6.14 (s, 1H), 4.63 (s, 2H), 4.56 (s, 2H), 2.58–0.93 (m, 30H); ^{13}C NMR ($CDCl_3$) δ 155.20, 148.56, 148.03, 123.05, 117.34, 107.53, 71.14, 56.62, 55.90, 55.60, 44.43, 44.37, 36.93, 36.18, 34.41, 29.28, 29.21, 28.63, 27.43, 25.40, 20.76, 19.03, 18.82, 18.59; IR ($CDCl_3$) 3608, 3443, 2355, 2319, 1267 cm^{-1}; UV (MeOH) λ_{max} 272 nm (ε = 30 600); $[\alpha]^{23}_D$ −22.3 (c = 0.08, CH_2Cl_2); HRMS m/z (M^+) calcd for $C_{24}H_{38}O_4$ 390.2770, found 390.2776.

C,D-Ring Diol 21. Into a solution of vitamin D_2 (2.0 g, 5.04 mmol) in CH_2Cl_2 (70 mL) and CH_3OH (15 mL) containing $NaHCO_3$ (28 mg) at −78 °C was bubbled ozone for a period of 60 min. Dry air was flushed through the reaction mixture for 15 min to remove the residual ozone. The reaction mixture was allowed to warm to 0 °C, and $NaBH_4$ (1.5 g, 40.0 mmol) was added portionwise for a period of 30 min. After the addition, stirring was continued for 2 h at room temperature. HCl (1 N) (20 mL) was added dropwise. The resulting reaction mixture was extracted with CH_2Cl_2, and the combined organic phase was washed once with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (30% EtOAc/hexanes) to afford 0.73 g (3.40 mmol, 68%) of the desired product as an oil. Spectroscopic data of this compound were identical to those reported in the literature.[18]

C,D-Ring Alcohol 22. To a stirred solution of C,D-ring diol **21** (0.70 g, 3.30 mmol), TBDMSCl (1.24 g, 8.25 mmol), and DMAP (101 mg, 0.83 mmol) in THF (20 mL) was added NEt_3 (1.15 mL, 8.25 mmol). The resulting reaction mixture was stirred at room temperature for 2 h and then refluxed for 12 h. The reaction mixture was allowed to cool to room temperature, the reaction quenched with saturated NH_4Cl solution, and the mixture extracted with ether. The combined organic phase was washed once with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (2% EtOAc/hexanes) to give 1.21 g (2.74 mmol) of the bissilylated diol intermediate. This was dissolved in THF (20 mL), and NEt_3 (1 mL) was added, followed by a 1.0 M n-Bu_4NF solution (2.74 mL, 2.74 mmol). The resulting reaction mixture was stirred at room temperature for 3 h and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (20% EtOAc/hexanes) to afford 0.77 g (2.36 mmol, 71%) of the desired product as an oil. Spectroscopic data of this compound were identical to those reported in the literature.[19]

20(*R*)-Epimer Alcohol 23. A mixture of alcohol **22** (437 mg, 1.34 mmol), PCC (578 mg, 2.68 mmol), and dry Celite (550 mg) in CH_2Cl_2 (20 mL) was stirred at room temperature for 1.5 h. The reaction mixture was passed through silica gel (8 g), eluting with a 1:1 mixture of hexanes/ether (60 mL), and evaporation of solvents under reduced pressure afforded 400 mg (1.23 mmol) of the corresponding aldehyde. This was dissolved in CH_2Cl_2 (6 mL), and a 40% n-Bu_4NOH aqueous solution (0.40 mL, 0.62 mmol) was added. The resulting reaction mixture was stirred at room temperature for 16 h, concentrated under reduced pressure, and chromatographed on silica gel (1% EtOAc/hexanes) to give 260 mg (0.82 mmol, 65%) of a 2:1 mixture of 20(*R*)- and 20(*S*)-aldehydes. This mixture was dissolved in THF (5 mL), and $NaBH_4$ (30 mg, 0.79 mmol) was added, followed by dropwise addition of EtOH (4 mL). The resulting reaction mixture was stirred at room temperature for 30 min, the reaction quenched with saturated NH_4Cl solution (10 mL), and the mixture extracted with ether. The combined organic phase was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (5% EtOAc/hexanes) to afford 147 mg (0.45 mmol, 37% from **22**) of the desirable 20(*R*)-epimer as an oil: ^{1}H NMR ($CDCl_3$) δ 4.03–3.97 (m, 1H), 3.71 (dd, J = 10.6 and 3.6 Hz, 1H), 3.45 (dd, J = 10.6 and 7.2 Hz, 1H), 1.90−1.07 (m, 13H), 0.94 (d, J = 6.8 Hz, 3H), 0.93 (s, 3H), 0.88 (s, 9H), 0.006 (s, 3H), −0.007 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 69.29, 66.83, 53.01, 52.96, 41.91, 40.12, 37.48, 34.39, 26.73, 25.80, 22.86, 18.03, 17.66, 16.60, 14.09, −4.79, −5.16; $[\alpha]^{23}_D$ +40.6 (c = 2.80, CH_2Cl_2); IR ($CHCl_3$), 3628, 2931, 2857, 2360, 1253, 1023, 903, 837, 746, 652 cm^{-1}; HRMS m/z (M^+ − t-Bu) calcd for $C_{19}H_{38}O_2Si$ 269.1937, found 269.1938.

C,D-Ring Diol 24. To a stirred solution of alcohol **23** (50 mg, 0.15 mmol) and 18-crown-6 (122 mg, 0.46 mmol) in THF (4 mL) at room temperature was added a 1.0 M KO-t-Bu solution (0.40 mL, 0.40 mmol) in t-BuOH, and the resulting reaction mixture was stirred at room temperature for 2 h before $Br(CH_2)_3CMe_2OTMS$[14b] (156 mg, 0.62 mmol) in THF (3 mL) was added via cannula. The resulting reaction mixture was stirred for 3 h at room temperature, the reaction quenched with saturated NH_4Cl solution, and the mixture extracted with ether. The combined organic phase was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (1% EtOAc/hexanes) to give 65 mg (0.13 mmol, 85%) of the O-alkylated intermediate. This was dissolved in THF (4 mL), and NEt_3 (0.5 mL) was added, followed by a 1.0 M n-Bu_4NF solution (1.2 mL, 1.2 mmol) in THF. The resulting reaction mixture was refluxed for 3 d, cooled to room temperature, and chromatographed on silica gel (30% EtOAc/hexanes) to afford 34 mg (0.11 mmol, 71% overall) of the desired diol as an oil: ^{1}H NMR ($CDCl_3$) δ 4.38–4.02 (m, 1H), 3.48 (dd, J = 9.2 and 4.0 Hz, 1H), 3.43–3.35 (m, 2H), 3.12 (dd, J = 9.2 and 7.6 Hz, 1H), 2.85−2.68 (br s, 1H), 1.85−1.05 (m, 23H), 0.93−0.85 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 74.98, 71.42, 70.03, 69.06, 53.50, 52.43, 41.60, 41.03, 39.67, 35.32, 33.48, 29.35, 29.14, 26.52, 24.70, 22.28, 17.39, 17.18, 13.81; $[\alpha]^{23}_D$ +9.67 (c = 1.50, CH_2Cl_2); IR ($CHCl_3$) 3616, 2937, 2871, 2244, 1455, 1375, 1099, 926, 899, 757, 727, 708 cm^{-1}; HRMS m/z (M^+) calcd for $C_{19}H_{36}O_3$ 312.2664, found 312.2670.

C,D-Ring 19b. The mixture of alcohol **24** (50 mg, 0.16 mmol), PCC (69 mg, 0.32 mmol), and dry Celite (70 mg) in CH_2Cl_2 (2 mL) was stirred for 2 h at room temperature. The resulting mixture was passed through silica gel (4 g), eluting with a 1:1 mixture of hexanes/ether (40 mL). Evaporation of solvents under reduced pressure afforded the crude ketone intermediate. This was dissolved in CH_2Cl_2 (0.5 mL), and (trimethylsilyl)imidazole (112 mg, 0.80 mmol) was added. The resulting reaction mixture was stirred overnight at room temperature, the reaction quenched with water, and the mixture extracted with ether. The combined organic phase was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (10% EtOAc/hexanes) to provide 58 mg (0.15 mmol, 94%) of the O-silylated C,D-ring ketone as an oil: ^{1}H NMR ($CDCl_3$) δ 3.44−3.29 (m, 3H), 3.21 (dd, J = 9.2 and 6.4 Hz, 1H), 2.44 (dd, J = 11.6 and 7.6 Hz, 1H), 2.30–2.15 (m, 2H), 2.04−1.30 (m, 12H), 1.20 (s, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.64 (s, 3H), 0.087 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 211.91, 74.85, 73.68, 71.46, 61.84, 53.54, 49.69, 41.25, 40.88, 38.08, 35.54, 29.84, 29.81, 26.67, 24.76, 23.94, 18.91, 17.24, 12.84, 2.58; $[\alpha]^{23}_D$ −40.0 (c = 1.60, CH_2Cl_2); IR ($CHCl_3$) 3154, 2967, 2876, 2284, 2239, 1790, 1698, 1250, 1036, 840 cm^{-1}; HRMS m/z (M^+) calcd for $C_{25}H_{40}O_2SSi$ 432.2518, found 432.2515.

C,D-Ring Diol 25. To a stirred solution of alcohol **23** (133 mg, 0.40 mmol) in THF (10 mL) at 0 °C was added a 1.0 M NaHMDS solution (0.60 mL, 0.60 mmol) in THF, and the resulting reaction mixture was stirred at room temperature for 30 min before TsCl (117 mg, 0.60 mmol) in THF (6 mL) was added via cannula. The resulting reaction mixture was stirred at room temperature for 2 h, the reaction quenched with saturated $NaHCO_3$ solution, and the mixture extracted with ether. The combined organic phase was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (10% EtOAc/hexanes) to give 150 mg (0.31 mmol, 79%) of the corresponding tosylate. To a stirred solution of m-[(1′,1′-dimethylhydroxy)methyl]thiophenol [15] (105 mg, 0.62 mmol) in DMF (6 mL) was added a 1.0 M KO-t-Bu solution (0.62 mL, 0.62 mmol) in THF, and the resulting solution was stirred for 2 h at room temperature before the above-prepared tosylate (150 mg, 0.31 mmol) in THF (4 mL) was added via cannula. The resulting reaction mixture was stirred at room temperature overnight, the reaction quenched with saturated NH_4Cl solution, and the mixture extracted with ether. The combined organic phase was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (5% EtOAc/hexanes) to afford the S-alkylated intermediate. This was dissolved in THF (4 mL), and NEt_3 (0.5 mL) was added, followed by a 1.0 M n-Bu_4NF solution (2.0 mL, 2.0 mmol) in THF. The resulting reaction mixture was refluxed for 3 d, cooled to room temperature, and chromatographed on silica gel (50% EtOAC/hexanes) to provide 87 mg (0.22 mmol, 60% overall) of **25** as an oil: ^1H NMR ($CDCl_3$) δ 7.41–7.37 (m, 1H), 7.21–7.08 (m, 3H), 4.00–3.94 (m, 1H), 3.54 (dd, J = 12.4 and 3.6 Hz, 1H), 2.61 (dd, J = 12.4 and 8.8 Hz, 1H), 2.09–2.04 (br s, 2H), 1.86–1.12 (m, 19H), 0.94 (d, J = 6.4 Hz, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.76, 137.34, 128.53, 127.15, 125.20, 121.83, 72.88, 69.05, 55.74, 52.32, 41.75, 40.48, 40.19, 34.66, 33.40, 31.61, 26.68, 22.23, 18.80, 17.40, 13.93; $[\alpha]^{23}{}_D$ −22.3 (c = 2.00, CH_2Cl_2); IR ($CHCl_3$) 3614, 2933, 2872, 2248, 1471, 1175, 909, 894, 746, 712, 649 cm^{-1}; HRMS m/z (M^+) calcd for $C_{22}H_{34}O_2S$ 362.2280, found 362.2276.

C,D-Ring 19c. The mixture of alcohol **25** (50 mg, 0.13 mmol), PCC (39 mg, 0.18 mmol), NaOAc (30 mg), and dry Celite in CH_2Cl_2 (5 mL) was stirred at 0 °C for 40 min. The reaction mixture was passed through silica gel (5 g), eluting with a 1:1 mixture of hexanes/ether (30 mL), and evaporation of solvents under reduced pressure gave the ketone intermediate, which was dissolved in CH_2Cl_2 (0.5 mL). (Trimethylsilyl)-imidazole (109 mg, 0.78 mmol) was added. The resulting reaction mixture was stirred overnight at room temperature, the reaction quenched with water, and the mixture extracted with ether. The combined organic phase was washed with brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (10% EtOAc/hexanes) to provide 40 mg (0.09 mmol, 67%) of (−)-**19c** as an oil: ^1H NMR ($CDCl_3$) δ 7.47–7.43 (m, 1H), 7.25–7.16 (m, 3H), 3.18 (dd, J = 12.0 and 3.6 Hz, 1H), 2.79 (dd, J = 12.0 and 8.0 Hz, 1H), 2.46 (dd, J = 11.6 and 7.6 Hz, 1H), 2.30–1.31 (m, 18H), 1.05 (d, J = 6.8 Hz, 3H), 0.58 (s, 3H), 0.094 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 211.48, 150.80, 136.50, 128.32, 127.31, 125.97, 122.44, 74.99, 61.57, 55.28, 49.65, 40.94, 40.76, 38.60, 34.66, 32.42, 32.24, 26.58, 23.91, 18.80, 18.76, 12.87, 2.36; $[\alpha]^{23}{}_D$ −53.4 (c = 1.05, CH_2Cl_2); IR ($CHCl_3$) 2965, 2254, 1706, 1382, 1252, 1219, 1040, 910, 842, 781, 774, 651 cm^{-1}; HRMS m/z (M^+) calcd for $C_{25}H_{40}O_2SSi$ 432.2518, found 432.2515.

Aromatic Analog 20a. Preparation of **20a** closely followed the procedure described for **2b**. The reagents and purification techniques are as follows: (1) coupling with bromobenzene **7** (87 mg, 0.19 mmol), t-BuLi (114 μL, 0.19 mmol, 1.7 M solution in pentane), C,D-ring ketone (−)-**19a**[16a] (14 mg, 0.03 mmol), and THF (2 mL) and silica gel column chromatography (0.1% NEt_3, 5% EtOAc/hexanes); (2) dehydration with tertiary alcohol from coupling (18 mg, 0.02 mmol), Burgess reagent (22 mg, 0.09 mmol) and benzene (4 mL) and silica gel chromatography (0.1% NEt_3, 1% EtOAc/hexanes); and (3) deprotection with olefin from dehydration (16 mg, 0.02 mmol), solid n-Bu_4NF (41 mg, 0.16 mmol), NEt_3 (50 μL, 0.36 μmol), and THF (5 mL) and silica gel column chromatography (0.1% NEt_3/EtOAc). This afforded 10 mg (0.02 mmol, 63% overall yield from (−)-**19a**) of the title compound as a gum: ^1H NMR ($CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 1.2 Hz, 1H), 7.14 (dd, J = 7.6 and 2.0 Hz, 1H), 5.69–5.65 (m, 1H), 4.73 (s, 2H), 4.72 (s, 2H), 3.65–1.00 (m, 24H), 1.10 (d, J = 6 Hz, 3H), 0.871 (t, J = 7.6 Hz, 3H), 0.865 (t, J = 7.6 Hz, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.40, 139.41, 138.91, 137.05, 129.34, 128.29, 126.77, 126.06, 78.31, 74.17, 68.83, 64.52, 64.11, 54.72, 49.22, 42.64, 35.69, 35.67, 31.11, 30.82, 25.74, 25.06, 24.59, 24.25, 18.29, 11.99, 7.90, 7.86; IR ($CHCl_3$) 3694, 3606, 3470, 2965, 2969, 2880, 1711, 1602, 1461, 1373, 1264, 1242, 1098, 1010 cm^{-1}; UV (MeOH) λ_{max} 248 nm (ϵ = 14 400); $[\alpha]^{32}{}_D$ −5.0 (c = 0.10, CH_2Cl_2); HRMS m/z (M^+) calcd for $C_{28}H_{44}O_4$ 444.3240, found 444.3230.

Aromatic Analog 20b. This was prepared by following the same procedure described for **2b**. The reagents utilized were as follows: **7** (105 mg, 0.23 mmol), t-BuLi (0.14 mL, 0.23 mmol, 1.7 M solution in pentane), C,D-ring (−)-**19b** (18 mg, 0.05 mmol), Burgess reagent (50 mg, 0.21 mmol), NEt_3 (30 μL), and n-Bu_4NF (0.14 mL, 0.14 mmol, 1.0 M solution in THF). This afforded 15 mg (0.03 mmol, 77% overall from (−)-**19b**) of the title compound as a gum: ^1H NMR ($CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 1.6 Hz, 1H), 7.12 (dd, J = 8.0 and 1.6 Hz, 1H), 5.67–5.61 (m, 1H), 4.69 (s, 2H), 4.68 (s, 2H), 3.56 (dd, J = 9.2 and 4.0 Hz, 1H), 3.49–3.15 (m, 4H), 2.80–2.08 (m, 3H), 1.97–1.19 (m, 20H), 0.96 (d, J = 6.4 Hz, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 143.22, 139.77, 138.93, 137.14, 129.30, 128.29, 126.73, 125.36, 75.32, 71.59, 70.19, 64.39, 63.98, 51.45, 49.74, 42.49, 41.16, 36.16, 35.36, 29.43, 29.22, 27.58, 25.01, 24.78, 24.29, 17.38, 11.69; IR ($CDCl_3$) 3589, 2954, 2931, 2340, 1709, 1210, 1120, 1011, 782, 758, 731 cm^{-1}; $[\alpha]^{23}{}_D$ +29.4 (c = 1.10, CH_2Cl_2); UV (MeOH) λ_{max} 248 nm (ϵ = 16 700); HRMS m/z (M^+) calcd for $C_{27}H_{42}O_4$ 430.3083, found 430.3080.

Aromatic Analog 20c. This was prepared by following the same procedure described for **2b**. The reagents utilized were as follows: **7** (98 mg, 0.22 mol), t-BuLi (0.13 mL, 0.22 mmol, 1.7 M solution in pentane), C,D-ring ketone (−)-**19c** (20 mg, 0.04 mmol), Burgess reagent (50 mg, 0.21 mmol), NEt_3 (30 μL), and n-Bu_4NF (0.11 mL, 0.11 mmol, 1.0 M solution in THF). This yielded 16 mg (0.03 mmol, 72% overall from (−)-**19c**) of the title compound as a gum: ^1H NMR ($CDCl_3$) δ 7.49–7.46 (m, 1H), 7.27–7.06 (m, 6H), 5.63–5.59 (m, 1H), 4.65 (s, 2H), 4.64 (s, 2H), 3.40–3.20 (m, 3H), 2.80 (dd, J = 12.0 and 8.8 Hz, 1H), 2.66–1.18 (m, 18H), 1.04 (d, J = 6.8 Hz, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.78, 143.10, 139.61, 138.89, 137.46, 137.11, 129.31, 128.64, 128.29, 127.16, 126.72, 125.31, 125.17, 121.89, 72.42, 64.32, 63.92, 53.59, 49.63, 42.62, 40.73, 35.89, 35.46, 31.68, 27.69, 25.00, 24.23, 18.97, 11.78; $[\alpha]^{23}{}_D$ −29.5 (c = 0.80, CH_2Cl_2); IR ($CDCl_3$) 3598, 3019, 2964, 2334, 1223, 1207, 1011, 788, 768, 748 cm^{-1}; UV(MeOH) λ_{max} 253 nm (ϵ = 22 100); HRMS m/z (M^+) calcd for $C_{30}H_{40}O_3S$ 480.2698, found 480.2689.

Acknowledgment. We thank the NIH for financial support, Professor Cecil H. Robinson (Department of Pharmacology, Johns Hopkins University) for a critical suggestion concerning aromatic analogs of steroids, Dr. Ron Horst (National Animal Disease Center, Ames, IA) for the calf thymus receptor binding studies, and Dr. Milan Uskoković (Hoffmann-La Roche) for a generous gift of C,D-ring ketone (+)-**17**.

Supporting Information Available: ^1H and ^{13}C NMR spectra (48 pages). Ordering information is given on any current masthead page.

References

(1) Robertson, D. W.; Katzenellenbogen, J. A. Synthesis of E and Z isomers of the antiestrogen tanoxifen and its metabolite, hydroxytamoxifen, in tritium-labeled form. *J. Org. Chem.* **1982**, *47*, 2387–2393, and references therein.

(2) Figadère, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura, W. H. Arocalciferols: synthesis and biological evaluation of aromatic side-chain analogues of 1α,25-dihydroxyvitamin D_3. *J. Med. Chem.* **1991**, *34*, 2452–2463.

(3) (a) Curtin, M. L.; Okamura, W. H. 1α,25-Dihydroxyprevitamin D_3: synthesis of the 9,14,19,19,19-pentadeuterio derivative and a kinetic study of its [1,7]-sigmatropic shift to 1α,25-dihydroxyvitamin D_3. *J. Am. Chem. Soc.* **1991**, *113*, 6958–6966. (b) VanAlstyne, E. M.; Norman, A. W.; Okamura, W. H. 7,8-Cis geometric isomers of the steroid hormone 1α,25-dihydroxyvitamin D_3. *J. Am. Chem. Soc.* **1994**, *116*, 6207–6216. (c) Okabe, M.; Garofalo, L. M. Effects of protecting groups on the previtamin D/vitamin D equilibrium. *Tetrahedron Lett.* **1995**, *36*, 5853–5856.

(4) (a) Perlman, K. L.; DeLuca, H. F. 1α-Hydroxy-19-nor-vitamin D C-22 aldehyde. A valuable intermediate in the synthesis of side chain modified 1α,25-dihydroxy-19-nor-vitamin D_3. *Tetrahedron Lett.* **1992**, *33*, 2937–2940. (b) Sicinski, R. R.; Perlman, K. L.; DeLuca, H. F. Synthesis and biological activity of 2-hydroxy and 2-alkoxy analogs of 1α,25-dihydroxy-19-norvitamin D_3. *J. Med. Chem.* **1994**, *37*, 3730–3738.

(5) Sabourin, E. T.; Onopchenko, A. A convenient synthesis of 4-ethynylphthalic anhydride *via* 2-methyl-3-butyn-2-ol. *J. Org. Chem.* **1983**, *48*, 5135–5137.

(6) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskoković, M. R. Stereocontrolled total synthesis of 1α,25-dihydroxycholecalciferol and 1α,25-dihydroxyergocalciferol. *J. Org. Chem.* **1986**, *51*, 3098–3108.

(7) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. Thermal reactions of alkyl *n*-carbomethoxysulfamate esters. *J. Org. Chem.* **1973**, *38*, 26–31, and references therein.
(8) Jones, R. G.; Gilman, H. The halogen-metal interconversion with organolithium compounds. *Org. React.* **1951**, *6*, 339–366.
(9) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley Interscience, 1992; pp 998–1002.
(10) Gschwend, H. W.; Rodriguez, H. R. Heteroatom-facilitated lithiations. *Org. React.* **1979**, *26*, 1–360.
(11) See: Posner, G. H. Organic reactions at alumina sufraces. *Angew. Chem., Int. Ed. Engl.* **1978**, *117*, 487–496.
(12) Dean, F. M. *Adv. Heterocycl. Chem.* **1982**, *30*, 166.
(13) Posner, G. H.; Nelson, T. D.; Guyton, K. Z.; Kensler, T. W. New vitamin D_3 derivatives with unexpected antiproliferative activity: 1-(hydroxymethyl)-25-hydroxyvitamin D_3 homologs. *J. Med. Chem.* **1992**, *35*, 3280–3287.
(14) (a) Calverley, M. J.; Binderup, L. Synthesis and biological evaluation of MC 1357, a new 20-epi-23-oxa-1α,25-dihydroxyvitamin D_3 analogue with potent non-classical effects. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1845–1848. (b) Binderup, L.; Latini, S.; Binderup, E.; Bretting, C.; Calverley, M.; Hansen, K. 20-Epivitamin D_3 analogues: a novel class of potent regulators of cell growth and immune responses. *Biochem. Pharmacol.* **1991**, *42*, 1569–1575.
(15) Grue-Sorensen, G.; Binderup, E.; Binderup, L. In *Vitamin D. A pleuripotent steroid hormone. Structural studies, molecular endocrinology and clinical applications*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; De Gruyter: Berlin, 1994; pp 75–76.
(16) (a) Posner, G. H.; White, M. C.; Dolan, P.; Kensler, T. W.; Yukihiro, Y.; Guggino, S. E. 1α,25-Dihydroxyvitamin D_3 hybrid analogs with structural changes at both the A-ring and the C,D-ring side-chain. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2919–2924. (b) Yukihiro, S.; Posner, G. H.; Guggino, S. E. Vitamin D_3 analogs stimulate calcium currents in rat osteosarcoma cells. *J. Biol. Chem.* **1994**, *269*, 23889–23893. (c) Posner, G. H.; Johnson, N. Stereocontrolled total synthesis of calcitriol derivatives: 1α,25-dihydroxy-2-(4′-hydroxybutyl)vitamin D_3 analogs of an osteoporosis drug. *J. Org. Chem.* **1994**, *59*, 7855–7861, and references therein. (d) Posner, G. H.; Lee, J. K.; Li, Z.; Takeuchi, K.; Guggino, S. E.; Dolan, P. E.; Kensler, T. W. 1α,25-Dihydroxyvitamin D_3 hybrid analogs with structural modifications at both the A-ring and the C,D-ring side chain, II. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2163–2168.
(17) Anzano, M. A.; Smith, J. M.; Uskoković, M. R.; Peer, C. W.; Mullen, L. T.; Letterio, J. J.; Welsh, M. C.; Shrader, M. W.; Logsdon, D. L.; Driver, C. L.; Brown, C. C.; Roberts, A. B.; Sporn, M. B. 1α,25-Dihydroxy-16-ene-23-yne-26,27-hexafluoro-cholecalciferol (Ro 24-5531), a new deltanoid (vitamin D analogue) for prevention of breast cancer in the rat. *Cancer Res.* **1994**, *54*, 1653–1656.
(18) Leyes, G. A.; Okamura, W. H. Effect of 3-methyl substitutents on the thermal [1,5]- and [1,7]-sigmatropic hydrogen shifts of vinylallenes and other seco steroids related to vitamin D: synthesis of 3-methyl- and 3,3-dimethyl-substituted analogues of 3-deoxy-1α,25-dihydroxyvitamin D_3. *J. Am. Chem. Soc.* **1982**, *104*, 6099–6105.
(19) Wulkovich, P. M.; Barcelos, F.; Batcho, A.; Sereno, J. F.; Baggiolini, E. G.; Hennesey, B. M.; Uskoković, M. R. Stereoselective total synthesis of 1α,25S,26-trihydroxycholecalciferol. *Tetrahedron* **1984**, *40*, 2283–2296.

JM9505573