Syntheses of 1-Alkyl-1,25-dihydroxyvitamin D_3

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1-Alkylated analogs of 1α,25-$(OH)_2D_3$ were synthesized to investigate the effect of the alkyl group on the A-ring conformation and the biological potency. The analogs were synthesized via two routes. In the first approach, alkylation of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) adduct of 1-oxoprovitamin D (**4**) was used as the key step to synthesize 1β-methyl-1α,25-dihydroxyprovitamin D_3 $(OH)_2D_3$ (**16a**) efficiently and stereoselectively. The photolysis of the provitamin D (**16a**), however, gave the desired previtamin D (**17a**) only as a minor product (<5%) and an unusual 1,10-bond cleavage product (**18a**) occurred in high yield (79%). As an alternative C(1)-epimeric pairs of 1-alkyl-1,25-$(OH)_2D_3$ were synthesized conveniently from 25-hydroxy-1-oxoprevitamin D_3 (**19**) by reaction with an alkyllithium followed by thermal isomerization. In the alkylation, the alkyllithium attacked the ketone preferentially from the side of the 3β-hydroxyl group to afford the 1β-alkyl-1α-hydroxy epimer in a 1.6–2.7 to 1 ratio over the 1α-alkyl-1β-hydroxy isomer. Introduction of a 1β-methyl group to 1α,25-$(OH)_2D_3$, shifted the equilibrium between the two chair conformations of the A-ring preferentially to the side of the α-form (4:1) and reduced considerably the activity to bind to the VDR.

Introduction

Vitamin D_3 undergoes two metabolic hydroxylations at C(25) and 1α before eliciting its biological function.[1a] The biological actions of 1α,25-dihydroxyvitamin D_3 (1α,25-$(OH)_2D_3$, **1a**) appear to be mediated through a hormone–receptor complex[1] which regulates gene expression in a manner analogous to the mechanism of action of classical steroid hormones,[2] such as glucocorticoids and estrogen. Contrary to those typical steroid hormones, vitamin D is a highly flexible molecule. The A-ring, seco-B-ring, and the side chain can adopt a wide range of conformations. Therefore it is important to know which conformation of vitamin D bind to the nuclear receptor (VDR)[3] and the serum vitamin D binding protein (DBP).[4] Such knowledge might clarify the mechanism of action of the hormone and help develop therapeutically useful vitamin D analogs. In our studies on the side chain conformation, we have shown evidence that the conformation responsible for the binding to both VDR and DBP is the anti form with respect to the C(17–20–22–23) torsion angle.[5] The present study was conducted to investigate the structure–activity relationship of the A-ring portion. It is not known whether a hydrophobic group introduced at the same carbon where the biologically important 1α-hydroxyl group is located has any effect on its biologic potency. In the case of the important 25-hydroxyl group the introduction of hydrophobicity around the hydroxyl group, such as perfluorination either at the 24,[6] or the 26- and 27-positions[7] and the introduction of an alkyl group to the 26 and/or 27 position,[8] has been known to elevate the biological potency. The A-ring part adopts two stable conformations, α-chair (Figure 1, **A**) where the

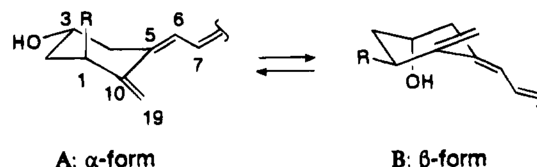

Figure 1.

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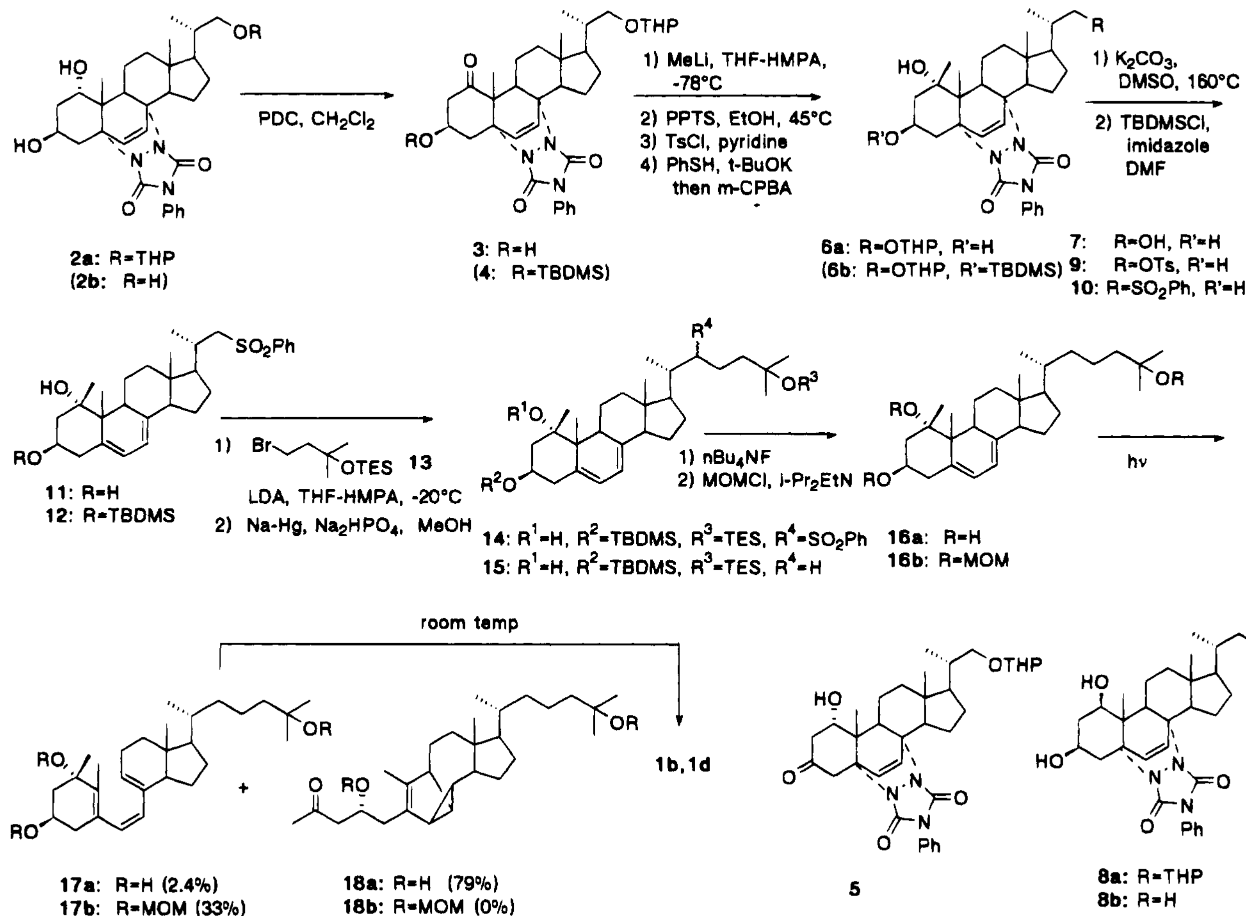
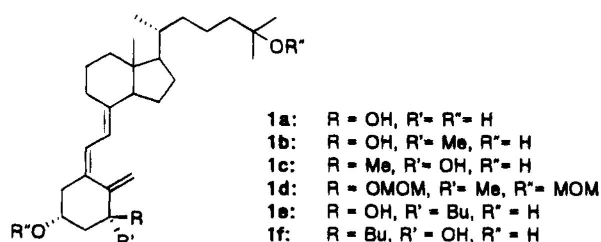
Scheme 1



10,19-exocyclic methylene is placed below the plane of the A-ring and the β-chair (**B**) where the methylene group is above the plane, as shown by X-ray crystallographic analysis,[9] photochemical reactivity,[10] NMR studies,[11] and force field calculations.[12] Therefore the effect of the 1-alkyl group upon the conformation of the A-ring as well as the biological activity was interesting. Recently a number of A-ring modified analogs that have shown useful biological activities have been reported, such as 2β-(hydroxypropoxy)-1α,25-(OH)$_2$D$_3$,[13] 19-nor-1α,25-(OH)$_2$-D$_3$,[14] 1β,25-(OH)$_2$D$_3$,[15] and 1-(hydroxyalkyl)-25-hydroxyvitamin D$_3$.[16] This paper reports the synthesis of 1α,25-(OH)$_2$D$_3$ analogs with an alkyl group at the 1-position (**1b**−**f**), the analysis of their A-ring conformation, and their potency to bind to the VDR.



Results and Discussion

1β-Methyl-1α,25-(OH)$_2$D$_3$ (**1b**) was synthesized via two routes. In the first approach (Scheme 1) the synthesis started with the readily available C$_{22}$ steroid (**2**).[17] The key step in the synthesis was the selective introduction

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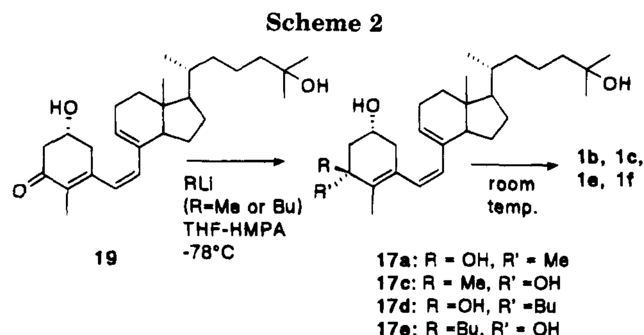
of a methyl group to the 1β-position. A methyl group can be introduced by the reaction of 1-keto steroids with MeLi. However, it has been reported that MeLi attacks preferentially from the α-face of the ketone in 1-oxocholesterol 3-TBDMS ether to yield the corresponding 1α-methyl 1β-alcohol as the major product (78% selectivity).[18] *We expected that if the 5,7-diene group is protected* with PTAD the α-face would be severely hindered and a β-face attack might predominate. The protection was also necessary to keep the diene group intact under the condition of oxidation with transition metal oxidants. The diol **2a** was treated with PDC to yield only 1-ketone **3** in good yield (70%). The preferential oxidation of an axial hydroxyl group over an equatorial one is well documented in the oxidation of steroidal alcohols by chromium reagents.[19] On the contrary, the oxidation of **3** under Swern's conditions gave only the 3-ketone **5** in high yield (79%). The reaction of the 1-ketone **3** with MeLi (THF–HMPA, −78 °C) gave a single methylated product (**6a**) in 94% yield. The unprotected 3β-hydroxyl group in **3** was shown to be important for the successful 1-alkylation. Under similar conditions (MeLi, THF–HMPA, −78 °C) the 3-protected 1-ketone **4** did not give the expected alkylation product **6b** but afforded a complex mixture of products. The stereochemistry at C(1) can be deduced by the ^{1}H NMR spectrum of the deprotected compound **7**. The H-3α resonance in **7** appears at lower field (δ 4.90) due to the effect of the axial 1α-hydroxyl group when compared with those compounds having no 1α-hydroxyl group, such as δ 4.91 for **2b** versus 4.51 for **8b**. The preferential β-face attack was also observed in the $NaBH_4$ reduction of **3** which gave **2a** and **8a** in 2:1 ratio (data not shown). The stereochemistry was confirmed by X-ray analysis of the crystalline derivative **12**.[20]

The desired side chain was introduced via the 22-sulfone **12**. The 22-hydroxyl group was converted to a phenylsulfonyl group via tosylate **9**, the PTAD was removed, and the 3-hydroxyl group was protected to afford **12**. Alkylation of the sulfone **12** with the bromide **13** gave **14** in high yield (90%). Removal of the phenylsulfonyl group followed by oxygen deprotection afforded the provitamin D **16a**.

With the desired provitamin D (**16a**) in hand we carried out the standard photochemical isomerization. To our surprise, **16a** did not undergo the usual photochemical electrocyclic reaction but yielded a previously unknown isomeric compound **18a** in high yield (79%).[21] The expected previtamin D (**17a**) was isolated only in a trace amount (2.4%) from a complex mixture of minor photoproducts by HPLC. The desired electrocyclic reaction became the major reaction when the 1α-hydroxyl group was protected, however the conversion rate of **16b** was 1/4 that of the unprotected provitamin D **16a**.[22] Thus the irradiation of tris-MOM ether **16b** gave the previtamin D **17b** as the major product (33% isolated yield based on the recovered starting material) with no abnormal photoproduct (**18b**) being detected. Both previtamins (**17a** and **17b**) were converted to the corresponding vitamin D (**1b** and **1d**) by thermal isomerization. Attempted deprotection of **1d**, however, was unsuccessful.[23]

Scheme 2



We then devised an alternative method that uses 25-hydroxy-1-oxoprevitamin D (**19**) as starting material. It is known that the allylic 1α-hydroxyl group of either 1α-hydroxylated vitamin D[24] or previtamin D[25] can be selectively oxidized (MnO_2[24a,25] or Dess–Martin reagent[24b]) to the corresponding 1-oxoprevitamin D in high yield. The reaction of ketone **19** with MeLi gave two isomeric methylated products, **17a** and **17c**, in 1.8:1 ratio (91% yield) (Scheme 2). The major product (**17a**) was determined to be the 1β-methyl-1α-hydroxy epimer by comparing the spectral data and HPLC behavior with those of **1b** obtained by the photolysis route, after being converted to the vitamin D (**1b**). The preferential β-face attack of the reagent can be explained by a chelation effect of the 3β-hydroxyl group.[26] The reaction with BuLi gave similarly two epimeric 1-butylated products, **17d** and **17e**, in 1.6:1 ratio (63%). The stereochemistry at C(1) of 1-butylated epimers was assigned by comparing their physical properties and spectral data with those of the 1-methylated derivatives. The cis 1β,3β-diols (**17c** and **17e**) are less polar than the corresponding trans 1α,3β-diols (**17a** and **17d**). This is probably because the *cis*-1,3-diol in the isomers **17c** and **17e** adopts a diaxial conformation as suggested by the ^{1}H NMR (**17c**: δ 4.20 (H-3), $W_{1/2}$ = 11.7 Hz). The previtamins underwent the thermal [1,7]-sigmatropic shift by standing at room temperature. The 1α-hydroxyl epimers **17a** and **17d** isomerized with a normal rate. But the isomerization rates of the 1β-hydroxy epimers **17c** and **17e** were considerably slower. At room temperature (25 °C) **17a** gave a 1:9 equilibrium mixture of previtamin D (**17a**) and vitamin D (**1b**) after 1 week, but the epimer (**17c**) had a half-life of about 3 weeks at same temperature. However

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(20) Crystal data: $C_{35}H_{54}O_4SSi$, FW = 598.35, space group $P2_12_12$ (orthorhombic), Z = 4, a = 13.340(1), b = 23.484(1), c = 11.304(3) Å, V = 3541.4(9) Å^3, D_x = 1.121 mg m^{-3}, final R = 0.0631 for 2465 reflections.

(21) The new photochemical isomerization of provitamin D resulting from the 1,10-bond cleavage was found to occur generally with provitamin D having 1α-hydroxyl group. Yamada, S.; Ishizaka, H.; Ishida, H.; Yamamoto, K. *J. Chem. Soc. Chem. Commun.* **1995**, in press.

(22) The relative rates were determined in EtOH solution (2.3 × 10^{-4} M) at 270–290 nm using an irradiation spectrophotometer (JASCO CRM-FD).

(23) Under the conditions of deprotection the triene part isomerized readily. Protection with either *tert*-butyldimethylsilyl or acetocyl groups was unsuccessful becuase the 1α-hydroxyl group is severely sterically hindered. Contrary to the reported results[18] acetylation of the provitamin D (**16a**) did not give the expected 1,3,25-triacetate. 3,25-Diacetate was obtained when a catalytic amount of DMAP (Ac_2O, pyridine, room temp) was used. Under forcing conditions (0.5–1.0 equiv of DMAP, Ac_2O, pyridine, 50 °C), a complex mixture of acetates, in which the acetoxy carbons were further acetylated, was obtained.

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(26) It has been reported that $NaBH_4$ reduction of 1-oxoprevitamin D gave exclusively 1β-hydroxyprevitamin D whereas $LiAlH_4$ reduction yielded both 1α- and 1β-hydroxyprevitamin D in 1:2.8 ratio. In the latter reaction, the coordination of the reagent with 3β-hydroxyl group was suggested to explain the formation of the 1α-hydroxy compound.[24a]

Table 1. ^1H NMR Spectra of 1-Alkyl-1,25-dihydroxyvitamin D_3[a]

	1b	1e	1c	1f
H-2α	2.14 (ddd, 1.8, 4.3, 13.1)	1.98 (dd, 4.3, 13.1)	2.00 (dd, 3.4, 13.7)	2.10 (ddd, 1.6, 4.3, 12.7)
H-2β	1.64 (dd, 9.2, 13.1)	1.84 (dd, 6.4, 13.1)	1.91 (dd, 3.7, 13.7)	1.73 (dd, 9.1, 12.7)
H-4α	2.65 (dd, 4.3, 12.2)	2.63 (dd, 4.3, 13.1)	2.56 (dd, 3.2, 13.3)	2.60 (dd, 4.3, 12.7)
H-4β	2.23 (dd, 9.2, 12.2)	2.29 (dd, 6.4, 13.1)	2.44 (dd, 4.9, 13.3)	2.28 (dd, 9.1, 12.7)
H-3α	4.15 (tt, 4.3, 9.2)	4.17 (m)	4.08 (m)	3.93 (tt, 4.3, 9.1)

[a] Chemical shifts are reported in ppm. Multiplicities and coupling constants (Hz) are within parentheses.

at 80 °C the pre-D to D equilibrium ratio was smaller for **17c** and **1c** (1:9) than for **17a** and **1b** (2:8). Steric congestion between the 1β-hydroxyl group and the C(11) methylene at the transition state of the [1,7]-sigmatropic hydrogen shift, where a right-handed helix conformation (A ring portion is placed below the CD ring part) is considered to be favored,[27] might be the cause of the reduced isomerization rate.

The A-ring conformation of the 1-alkylvitamin D was studied by ^1H NMR spectroscopy (Table 1). Introduction of a methyl at the 1β-position makes the α-form energetically more favorable. While the proportion of the α- and β-forms in 1α,25-$(OH)_2D_3$ is reported to be about 1:1,[11] the ratio in 1β-methyl-1α,25-$(OH)_2D_3$ (**1b**) was 4:1 as calculated by the coupling constant between H-4β and H-3α.[28] This is in good agreement with the ratio calculated by molecular mechanics:[29] the steric energy difference between the α- and β-forms of **1b** is about 1 kcal and the corresponding Boltzmann distribution at 25 °C is 85:15. In the 1β-butylated derivative **1e** the proportion of the α- and β-forms was again comparable (45:55).

Preliminary biological evaluation showed that the activity of the analog **1b** in binding to calf thymus receptor[30] was about 1/150 relative to 1α,25-$(OH)_2D_3$ (**1a**) and those of the others (**1c,e,f**) were less than 1/1000 . Thus, the introduction of only a methyl group at the 1β-position was found to severely mask the function of the 1α-hydroxyl group. As described above, the stable conformation of **1b** is the α-form where the 1α-hydroxyl group adopts an axial orientation. Therefore, if the β-form is responsible for VDR binding,[31] the weak potentiality might in part be ascribed to the conformation.

Recently Posner[16] reported that the antiproliferative activities of 1α- and 1β-(hydroxymethyl)-25-hydroxyvitamin D_3 were similar to that of the active vitamin D_3 (**1a**), though their activities to bind to VDR were less than 1/1000 relative to **1a**. Since the competitive binding assay alone cannot properly evaluate the biological potency, further studies, such as expression of m-RNA of VDR-mediated genes and in vitro differentiation activity measurements, are necessary. These studies are now under investigation.

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(28) The composition was calculated using J_{axax} = 11.1, and J_{eqeq} = 2.7 Hz. (Anet, F. A. L. *J. Am. Chem. Soc.* **1962**, *84*, 1053–1054. See also ref 11).

(29) Calculated by MMX using software PCMODEL (Serena Software, Bloomington, IN). MMX is an enhanced version of MM2 (Gajewski, J. J.; Gilbert K. E.; McKelvey J. *Adv. Mol. Model.* **1990**, *2*, 65–92).

(30) The activity of the analogs to bind to VDR was determined by using commercially available calf thymus receptor kit (Yamasa Biochemical, Chiba, Japan) as described: Imae, Y.; Manaka, A.; Yoshida, N.; Ishimi, Y.; Shinki, T.; Abe, E.; Suda, T.; Konno, K.; Takayama, H.; Yamada, S. *Biochim. Biophys. Acta* **1994**, *1213*, 302–308.

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Experimental Section

General. ^1H NMR spectra were measured at 270 or 500 MHz on commercially available instruments. Low and high resolution mass spectra were measured at 70 eV. Relative intensities are given in parentheses. IR spectra were recorded on commercially available FT-IR instruments in either transmission or reflection mode. All air-sensitive reactions were run under argon atmosphere, and reagents were added through septa using oven-dried syringes. The phrase "dried and evaporated" indicates drying with $MgSO_4$, followed by evaporation of the solvents under house vacuum.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of 3β-Hydroxy-22-(tetrahydropyranyloxy)-23,24-dinor-5,7-choladien-1-one (3). To a solution of the adduct **2a** (634 mg, 1.05 mmol) in dry CH_2Cl_2 (14 mL) were added Celite (15 g) and pyridinium dichromate (PDC) (473 mg, 1.26 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with Et_2O, the insoluble inorganic solid was filtered off, and the solvent was evaporated. The residue was chromatographed on silica gel (35 g) with hexane–EtOAc (3:7) to give ketone **3** (444 mg, 70%): ^1H NMR ($CDCl_3$) δ 0.82 and 0.83 (1:1) (3 H, s), 1.08 and 1.09 (1:1) (3 H, d, J = 6.4 Hz), 1.21 (3 H, s), 4.77 (1 H, m), 6.27 and 6.52 (each 1 H, d, J = 8.4 Hz), 7.37 (5 H, m); MS m/z 428 (M^+ – PTAD, 4), 410 (4), 326 (9), 119 (45), 85 (100); IR (KBr) 2948, 1758, 1711, 1404, 1033, 754 cm^{-1}.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of 1α-Hydroxy-22-(tetrahydropyranyloxy)-23,24-dinor-5,7-choladien-3-one (5). To a solution of oxalyl chloride (136 mg, 1.07 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C was added DMSO (126 μL, 1.8 mmol) in CH_2Cl_2 (0.5 mL). To the solution was added $NaHCO_3$ (45 mg, 0.54 mmol), and then a solution of **2a** (430 mg, 0.7 mmol) in CH_2Cl_2 (2 mL) and the mixture was stirred for 15 min at –78°C. Et_3N (396 μL, 2.8 mmol) was added to the mixture, and the resulting reaction mixture was allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2, washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel (40 g) with MeOH–$CHCl_3$ (3:7) to give **5** (333 mg, 79%). The ketone **5** is relatively unstable and a portion decomposed during chromatography; therefore, the spectra include some impurities: ^1H NMR ($CDCl_3$) δ 0.90 (3 H, s,), 1.03 (3 H, s,), 1.07 (3 H, d, J = 6.4 Hz), 2.83 (1 H, d, J = 18.3 Hz), 6.29 and 6.56 (each 1 H, d, J = 7.9 Hz), 7.36 (5 H, m). MS m/z 426 (M^+ – 177, 3), 342 (18), 177 (30), 119 (57), 85 (100).

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of 1β-Methyl-22-(tetrahydropyranyloxy)-23,24-dinor-5,7-choladiene-1α,3β-diol (6a). To a stirred solution of ketone **3** (500 mg, 0.83 mmol) in dry THF (12 mL) at –78 °C were added HMPA (432 μL, 2.49 mmol) and MeLi (1.4 M in Et_2O, 1.9 mL, 2.07 mmol). After 15 min, the mixture was quenched with aqueous NH_4Cl and extracted with AcOEt. The organic layer was washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel (35 g, 2% MeOH–$CHCl_3$) to give **6a** (363 mg, 70%) and **3** (125 mg, 25%). **6a**: ^1H NMR ($CDCl_3$) δ 0.87 and 0.88 (1:1) (3 H, s), 1.00 (3 H, s), 1.06 (3 H, d, J = 6.4 Hz), 1.16 (3 H, s), 4.91 (1 H, m), 6.33 and 6.38 (each 1 H, d, J = 8.4 Hz), 7.25–7.43 (5 H, m); MS m/z 444 (M^+ – PTAD, 2), 426 (2), 356 (2), 85 (100); IR (neat) 3413, 2945, 2873, 1742, 1683, 1503, 1408, 1116, 1022, 753 cm^{-1}.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of 1β-Methyl-23,24-dinor-5,7-choladiene-1α,3β,22-triol (7). To a solution of **6a** (7.57 g, 0.012 mol) in EtOH (70 mL) was added pyridinium p-toluenesulfonate (PPTS) (4.6 g, 0.018 mol), and the mixture was stirred at 45 °C for 2.5 h. Water was added

and the mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel (150 g, 5% MeOH–$CHCl_3$) to give **7** (5.6 g, 87%): mp 203–205 °C (colorless needles from acetone); ^1H NMR ($CDCl_3$) δ 0.87 (3 H, s), 0.99 (3 H, s), 1.06 (3 H, d, J = 6.4 Hz), 1.13 (1 H, s), 4.90 (1 H, m), 6.33 and 6.34 (each 1 H, d, J = 8.4 Hz), 7.25–7.43 (5 H, m); MS *m/z* 360 (M^+ – PTAD, 9), 342 (7), 324 (4), 272 (14), 119 (100); IR (KBr) 2956, 1744, 1684, 1415, 1031, 756 cm^{-1}; HRMS *m/z* calcd for $C_{31}H_{41}O_5N_3$ 535.3048 (M^+), found 535.3046 xb1 0.0004.

4-Phenyl-1,2,4-triazoline-3,5-dione Adduct of 1β-Methyl-22-(phenylsulfonyl)-23,24-dinor-5,7-choladiene-1α,3β-diol (10). To a solution of **7** (5.6 g, 0.01 mol) in dry pyridine (20 mL) was added TsCl (2.2 g, 0.012 mol) at 0 °C, and the mixture was stirred at that temperature. After 3 h, the reaction mixture was diluted with AcOEt and poured into ice-water. The organic layer was washed with water, 3% HCl, 5% $NaHCO_3$ and brine, dried, and evaporated. The residue was chromatographed on silica gel (150 g, 4% MeOH-$CHCl_3$) to give 3,22-ditosylate (0.6 g, 6%), **9** (4.9 g, 68%), and **7** (0.5 g, 10%). **9:** ^1H NMR ($CDCl_3$) δ 0.82 (3 H, s), 0.98 (3 H, s), 1.03 (3 H, d, J = 6.4 Hz), 1.13 (3 H, s), 2.44 (3 H, s,), 3.73 (1 H, dd, J = 6.9 and 8.9 Hz), 4.04 (1 H, dd, J = 3.2 and 8.9 Hz), 4.89 (1 H, m), 6.32 (2 H, s), 7.26 (7 H, m), 7.78 (2 H, m,); IR (KBr) 2950, 1744, 1688, 1408, 1178 cm^{-1}.

A solution of PhSH (733 μL, 7.14 mmol) and t-BuOK (801 mg, 7.14 mmol) in dry DMF (20 mL) was added to a stirring solution of **9** (4.1 g, 5.95 mmol) in dry DMF (10 mL) at 0 °C. After 30 min, water was added and the mixture was extracted with AcOEt. The organic layer was washed with water and 5% $NaHCO_3$, dried, and evaporated. The residue was dissolved in dry CH_2Cl_2 (30 mL), m-CPBA (2.68 g, 0.012 mol) was added at 0 °C, and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2, washed with 5% $NaHCO_3$ and brine, dried, and evaporated. The residue was chromatographed on silica gel (150 g, 4% MeOH-$CHCl_3$) to give **10** (3.63 g, 93% from **9**): mp 250–253 °C (acetone); ^1H NMR ($CDCl_3$) δ 0.85 (3 H, s), 0.97 (3 H, s), 1.09 (3 H, s), 1.23 (3 H, d, J = 6.4 Hz), 2.70 (1 H, dd, J = 12.4 and 6.9 Hz), 2.86 (1 H, dd, J = 8.9 and 13.9 Hz), 3.04 (1 H, dd, J = 14.3 and 5.4 Hz), 3.14 (1 H, d, J = 13.9 Hz), 4.86 (1 H, m), 6.31 (2 H, s), 7.29–7.42 (5 H, m), 7.54–7.68 (3 H, m), 7.90 (2 H, d, J = 6.9 Hz); MS *m/z* 484 (M^+ – PTAD, 6), 466 (10), 448 (8), 396 (22), 119 (100); IR (neat) 3594, 3517, 2934, 2867, 1744, 1682, 1412, 1298, 1143, 1084, 1020, 731 cm^{-1}; HRMS *m/z* calcd for $C_{29}H_{40}O_4S$ 484.2649 (M^+ – PTAD), found 484.2653 xb1 0.0005. Anal. Calcd for $C_{37}H_{45}O_6N_3S$: C, 67.35; H, 6.88; N, 6.37. Found: C, 67.11; H, 6.80; N, 6.51.

1β-Methyl-22-(phenylsulfonyl)-23,24-dinor-5,7-choladiene-1α,3β-diol (11). A solution of **10** (3.63 g, 5.51 mmol) and K_2CO_3 (6.8 g, 0.05 mol) in DMSO (70 mL) was stirred at 160 °C for 2.5 h. After being cooled, the reaction mixture was diluted with AcOEt and water and extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (90 g, 2.5% MeOH–$CHCl_3$) to give **11** (2.1 g, 79%): ^1H NMR ($CDCl_3$) δ 0.58 (3 H, s), 1.12 (3 H, s), 1.16 (3 H, s), 1.20 (3 H, d, J = 6.4 Hz), 3.88 (1 H, m), 5.21 and 5.74 (each 1 H, m), 7.54–7.68 (3 H, m), 7.91 (2 H, d, J = 6.9 Hz); MS *m/z* 484 (M^+, 13), 466 (22), 448 (17), 396 (39), 157 (100); IR (KBr) 2946, 2874, 1448, 1305, 1147, 1087, 540 cm^{-1}; HRMS *m/z* calcd for $C_{29}H_{40}O_4S$ 484.2649 (M^+), found 484.2642 xb1 0.0005.

3β-[(*tert*-Butyldimethylsilyl)oxy]-1β-methyl-22-(phenylsulfonyl)-23,24-dinor-5,7-choladien-1α-ol (12). To a solution of imidazole (827 mg, 0.012 mol) and **11** (1.96 g, 4.05 mmol) in dry DMF (9 mL) was added a solution of *tert*-butyldimethylsilyl chloride (916 mg, 6.07 mmol) in dry DMF (5 mL) at room temperature, and the mixture was stirred at that temperature for 40 min. The reaction mixture was quenched with water and extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (70 g, 1% MeOH–$CHCl_3$) to give **12** (2.1 g, 87%): mp 214–216 °C (acetone); ^1H NMR ($CDCl_3$) δ 0.05 (6 H, s), 0.58 (3 H, s), 0.88 (9 H, s), 1.10 (3 H, s,), 1.15 (3 H, s), 1.20 (3 H, d, J = 6.4 Hz), 3.82 (1 H, m), 5.20 and 5.71 (each 1 H, m), 7.54–7.68 (3 H, m), 7.91 (2 H, m); MS *m/z* 580 (M^+ – H_2O, 5), 523 (19), 449 (14), 448 (14), 201 (60), 73 (100); IR (KBr) 3490, 2954, 2860, 1303, 1149, 1089, 1065, 837, 779 cm^{-1}; HRMS *m/z* calcd for $C_{35}H_{54}O_4SSi$ 598.3514 (M^+), found 598.3516 xb1 0.0004.

3β-[(*tert*-Butyldimethylsilyl)oxy)]-1β-methyl-22-(phenylsulfonyl)-25-[(triethylsilyl)oxy]-5,7-cholestadien-1α-ol (14). To a stirred solution of diisopropylamine (352 μL, 2.51 mmol) and **12** (500 mg, 0.84 mmol) in dry THF (4 mL) at –20 °C was added dropwise a solution of n-BuLi (1.6 M in hexane, 1.57 mL, 2.51 mmol). After 10 min, a solution of 4-bromo-2-methylbutan-2-ol triethylsilyl ether (**13**, 702 mg, 2.51 mmol) and HMPA (873 μL, 5.02 mmol) in THF (3 mL) was added at –20 °C, and the mixture was stirred at that temperature for 45 min. The reaction mixture was quenched with aqueous NH_4Cl and extracted with EtOAc. The extracts were washed with water and brine, dried, and evaporated. The residue was chromatographed on silica gel (40 g, 15% EtOAc–hexane) to give **14** (less polar epimer, 520 mg, 78% and more polar epimer, 79 mg, 12%): less polar epimer: ^1H NMR ($CDCl_3$) δ 0.051 and 0.055 (each 3 H, s), 0.49 (3 H, s), 0.54 (6 H, q, J = 7.9 Hz), 0.88 (9 H, s), 0.93 (9 H, t, J = 7.9 Hz), 1.07 (3 H, d, J = 6.4 Hz), 1.10 (3 H, s), 1.15 (9 H, s), 3.82 (1 H, m), 5.19 and 5.71 (each 1 H, m), 7.51–7.87 (3 H, m), 7.87 (2 H, d, J = 6.9 Hz); MS *m/z* 780 (M^+ – H_2O, 3), 723 (11), 667 (3), 649 (6); IR (KBr) 2954, 2876, 1146, 1087, 837, 724 cm^{-1}; more polar epimer: ^1H NMR ($CDCl_3$) δ 0.064 (6 H, s), 0.45 (6 H, q, J = 7.5 Hz), 0.59 (3 H, s), 0.85 (9 H, t, J = 7.5 Hz), 0.89 (9 H, s), 1.08 (3 H, s), 1.09 (3 H, s), 1.13 (3 H, s), 1.17 (3 H, s), 1.34 (1 H, d, J = 6.9 Hz), 3.86 (1 H, m), 5.24 and 5.73 (each 1 H, d, J = 5 Hz), 7.26–7.65 (3 H, m), 7.88 (2H, d, J = 6.9 Hz); MS *m/z* 780 (M^+ – H_2O, 2), 723 (10), 667 (5), 649 (7).

3-[(*tert*-Butyldimethylsilyl)oxy]-1β-methyl-25-[(triethylsilyl)oxy]-5,7-cholestadien-1α-ol (15). To a solution of **14** (409 mg, 0.51 mmol) and Na_2HPO_4 (728 mg, 5.1 mmol) in MeOH (20 mL) was added 8.4% Na–Hg (1.4 g, 5.1 mmol) at 0 °C, and the mixture was stirred at that temperature for 5 m and at room temperature for 3 h. Ice–water was added and the mixture was extracted with EtOAc. The extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (35 g, 5% EtOAc–hexane) to give **15** (206 mg, 61%) and **14** (115 mg, 28%). **15**: ^1H NMR ($CDCl_3$) δ 0.059 and 0.062 (each 3 H, s), 0.56 (6 H, q, J = 7.9 Hz), 0.60 (3 H, s), 0.88 (9 H, s), 0.942 (3 H, d, J = 6.4 Hz), 0.945 (9 H, t, J = 7.9 Hz), 1.11 (3 H, s), 1.17 (3 H, s), 1.18 (6 H, s), 3.83 (1 H, m), 5.23 (1 H, m), 5.73 (1 H, m); IR (KBr) 2958, 1462, 1379, 1257, 1089, 1048, 837, 777, 741 cm^{-1}; MS *m/z* 583 (M^+ – 75, 9), 508 (7), 201 (49), 173 (54), 103 (76), 75 (100); HRMS *m/z* calcd for $C_{40}H_{74}O_3Si_2$ 658.5179 (M^+), found 658.5181 xb1 0.0005.

1β-Methyl-5,7-cholestadiene-1α,3β-25-triol (16a). To a solution of **15** (164 mg, 0.25 mmol) in dry THF (3 mL) was added n-Bu_4NF (1.0 M in THF, 3.5 mL, 3.5 mmol) at 0 °C, and the mixture was stirred at room temperature for 7 h. Aqueous NH_4Cl was added, and the mixture was extracted with EtOAc. The extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (25 g, 4% MeOH–$CHCl_3$) to give provitamin D **16a** (73 mg, 68%): mp 160–161 °C (acetone); ^1H NMR ($CDCl_3$) δ 0.60 (3 H, s), 0.93 (3 H, d, J = 6.4 Hz), 1.14 (3 H, s), 1.18 (3 H, s), 1.21 (6 H, s), 3.80–3.95 (1 H, m), 5.24 (1 H, m), 5.76 (1 H, m); UV (95% EtOH) 272, 282 293 nm; MS *m/z* 430 (M^+, 11), 412 (12), 394 (10), 157 (65), 145 (55), 59 (100); IR (contains acetone of crystallization) (KBr) 3506, 3400, 2962, 2872, 1715, 1377, 1263, 1029 cm^{-1}.

1β-Methyl-5,7-cholestadiene-1α,3β-25-triol Tris(methoxymethyl) Ether (16b). To a solution of triol **16a** (168 mg, 0.39 mmol) in CH_2Cl_2 was added diisopropylethylamine (6.1 mL, 35 mmol) and then MOMCl (1.78 mL, 23 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h, diisopropylamine (2 mL) and MOMCl (0.55 mL) were added, and stirring was continued for additional 15 h at room temperature. Water was added, and the mixture was extracted with CH_2Cl_2, washed with 1% HCl, 5% $NaHCO_3$, and brine, dried, and evaporated. The residue was chromatographed on silica gel (15 g) with EtOAc/hexane (1:4) to give MOM ether **16b**

(172 mg, 78%): ^{1}H NMR ($CDCl_3$) δ 0.61 (3 H, s), 0.93 (3H, d, J = 6.4 Hz), 1.15 (3 H, s), 1.21 (9 H, s), 3.36 (3 H, s), 3.37 (3 H, s), 3.39 (3 S, s), 3.80 (1 H, m), 4.65–4.82 (6 H, m), 5.24 (1 H, m), 5.61 (1 H, m); MS m/z 500 (M^+ − MOMOH, 7), 423 (56), 365 (22), 337 (100); IR (neat) 2945, 2883, 1466, 1378, 1210, 1145, 1096, 1042, 917 cm^{-1}; UV (95% EtOH) 271, 282, 294 nm.

Irradiation of 1β-Methyl-5,7-cholestadiene-1α,3β-25-triol (16a) and Synthesis of 1α,25-Dihydroxy-1β-methylvitamin D_3 (1b). A solution of the provitamin D **16a** (50 mg, 0.12 mmol) in EtOH (170 mL) was flushed with Ar for 15 min and then irradiated at 0 °C under Ar with a 100-W high-pressure mercury lamp (Shigemi Standard, Tokyo) through a Vycor filter until most of the provitamin D was consumed (5 min). The solvent was evaporated and the residue was chromatographed on Sephadex LH-20 (20 g, hexane:$CHCl_3$: MeOH = 30:70:0.5) to give **18a**[21] (39.5 mg, 79%) and then previtamin D **17a** (UV 262 nm) (1.2 mg, 2.4%, calculated using the ϵ (9000) of previtamin D_3). The previtamin **17a** was dissolved in 95% ethanol (10 mL) and stored in the dark at room temperature under Ar for 12 days. The solvent was evaporated, and the residue was chromatographed on Sephadex LH-20 with the same system as above to give **1b** (0.9 mg): ^{1}H NMR ($CDCl_3$) δ 0.53 (3 H, s), 0.93 (3 H, d, J = 6.4 Hz), 1.21 (6 H, s,), 1.46 (3 H, s), 4.15 (1 H, tt, J = 9.2 and 4.3 Hz), 4.94 and 5.32 (each 1 H, d, J = 1.5 Hz), 5.93 and 6.41 (each 1 H, d, J = 11.3 Hz); MS m/z 430 (M^+, 3), 412 (23), 394 (28), 379 (10), 376 (12), 361 (8), 265 (18), 169 (49), 166 (41), 155 (100), 151 (92); UV (95% EtOH) 264.6 nm, 252 nm (sh); IR (neat) 3366, 2937, 2870, 1467, 1377, 1148, 1086, 1037, 912, 895 cm^{-1}. **18a**: ^{1}H NMR ($CDCl_3$) δ 0.63 (3 H, s), 0.86 (3 H, d, J = 6.4 Hz), 1.21 (6 H, s), 1.55 (3 H, s), 2.18 (3 H, s), 2.5 (1 H, dd, J = 17.5 and 9 Hz), 2.97 (1 H, t, J = 7 Hz); MS m/z 430 (M^+, 4%), 343 (30), 325 (15), 107 (76); IR (KBr) 3448, 2938, 1710, 1383 cm^{-1}.

Irradiation of 1β-Methyl-5,7-cholestadiene-1α,3β-25-triol Tris(methoxymethyl) Ether (16b) and Synthesis of 1α,25-Dihydroxy-1β-methylvitamin D_3 Tris(methoxymethyl) Ether (1d). A solution of **16b** (47 mg, 8.4 × 10^{-5} mol) in EtOH (170 mL) was irradiated as described above for 12 min. The residue was purified by HPLC (column, YMC-Pack ODS-AM, 150 × 20 mm; solvent 5% H_2O/MeOH 10 mL/min) to give previtamin D **17b** (9.3 mg, 20%) and recovered **16b** (19 mg, 40%). The previtamin D **17b** was stored in EtOH at room temperature for 14 days, the solvent was evaporated, and the residue was chromatographed on silica gel (5 g) with EtOAc/hexane (1:4) to give vitamin D **1d** (7 mg, 75%): ^{1}H NMR ($CDCl_3$) δ 0.49 (3 H, s), 0.92 (3 H, d, J = 6.4 Hz), 1.21 (6 H, s), 1.46 (3 H, s), 3.31, 3.37, and 3.39 (each 3 H, s), 4.05 (1 H, m), 4.32 and 4.65 (each 1 H, d, J = 6.9 Hz), 4.71 (4 H, s), 5.14 and 5.34 (each 1 H, d, J = 1.5 Hz), 5.94 and 6.32 (each 1 H, d, J = 11.5 Hz); MS m/z 500 (M^+ − MOMOH, 20), 438 (52), 376 (100), 361 (22), 265 (31), 155 (76), 130 (47); IR (neat) 2929, 2856, 1463, 1367, 1252, 1146, 1096, 1036, 918, 835 cm^{-1}; UV (95% EtOH) 243, 266 nm.

Reaction of 25-Hydroxy-1-oxovitamin D_3 (19) with MeLi and Synthesis of 1α,25-Dihydroxy-1β-methylvitamin D_3 (1b) and 1β,25-Dihydroxy-1α-methylvitamin D_3 (1c). To a solution of 1-ketone **19**[24b] (16 mg, 3.86 × 10^{-5} mol) in THF (1 mL) and HMPA (34 μL) was added at −78°C a solution of MeLi (1.4 M, 138 μL, 1.93 × 10^{-4} mol, 5 equiv). Five min later, MeLi (138 μL) and HMPA (34 μL) were added, and the solution was stirred for 10 min at that temperature. Saturated NH_4Cl solution was added, and the mixture was extracted with ethyl acetate. The organic extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (5 g) with benzene−EtOAc (2: 8) to give **17c** (4.1 mg, 25%) and **17a** (10.9 mg, 66%) successively. **17a**: UV (95% EtOH) 262.4 nm; MS m/z 430 (M^+, 2), 412 (12), 394 (15), 379 (7), 361 (4), 265 (8), 166 (31), 155 (43), 151 (69). **17c**: UV (95% EtOH) 255.8 nm; MS m/z 430 (M^+, 1), 412 (15), 394 (13), 379 (6), 361 (4), 265 (8), 166 (29), 155 (36), 151 (52). The previtamin Ds were stored in EtOH at room temperature under argon. After 3 weeks, about a half of **17c** was converted to **1c** (1.6 mg) which was isolated by HPLC (YMC-Pack ODS-AM, 25% H_2O/MeOH). After 2 weeks **17a** gave an equilibrium mixture (1:9) of **17a** and **1b** from which **1b** (9.3 mg, 85%) was isolated by chromatography on silica gel (benzene/EtOAc, 2:8). **1c**: ^{1}H NMR ($CDCl_3$) δ 0.54 (3 H, s), 0.94 (3 H, d, J = 6.4 Hz), 1.22 (6 H, s), 1.39 (3 H, s), 4.08 (1 H, m), 4.95 and 5.32 (each 1 H, d, J = 1.5 Hz), 5.98 and 6.41 (each 1 H, d, J = 11 Hz); MS m/z 430 (M^+, 3), 412 (32), 394 (20), 379 (10), 265 (12), 166 (59), 155 (54), 151 (100); UV (95% EtOH) 262 nm; IR (neat) 3371, 2927, 2852, 1557, 1467, 1378, 1129, 1104, 936, 912 cm^{-1}.

Reaction of 25-Hydroxy-1-oxovitamin D_3 (19) with BuLi and Synthesis of 1β-Butyl-1α,25-dihydroxyvitamin D_3 (1e) and 1α-Butyl-1β,25-dihydroxyvitamin D_3 (1f). The ketone **19** (20 mg, 4.8 × 10^{-5} mol) in THF (500 μL) and HMPA (39 μL) was similarly treated with BuLi (1.6 M hexane solution, 139 μL, 2.22 × 10^{-4} mol, 4 equiv). After similar workup and chromatography, less polar alcohol **17e** (5.8 mg) and more polar alcohol **17d** (9.2 mg) were obtained. **17d**: UV (95% EtOH) 261 nm; MS m/z 454 (M^+ − H_2O, 10), 436 (6), 415 (12), 397 (12), 379 (7), 155 (43), 151 (100). **17e**: UV (95% EtOH) 255 nm; MS m/z 454 (M^+ − H_2O, 16), 436 (8), 415 (8), 397 (7), 155 (34), 151 (100). The previtamins were stored in EtOH for 18 days. Chromatographic purification on silica gel of the product from **17d** gave **1e** (7.6 mg, 83%) together with a trace of **17d**, and that from **17e** gave **1f** (2.6 mg, 45%) and **17e** (2.5 mg). **1e**: ^{1}H NMR ($CDCl_3$) δ 0.54 (3 H, s), 0.90 (3 H, t, J = 7.3 Hz), 0.93 (3 H, d, J = 6.2 Hz), 1.21 (6 H, s), 4.17 (1 H, m), 4.99 and 5.30 (each 1 H, d, J = 1.2 Hz), 5.96 and 6.36 (each 1 H, d, J = 11.6 Hz); MS m/z 472 (M^+, 2), 454 (18), 436 (10), 415 (12), 397 (9), 379 (8), 361 (5), 307 (5), 197 (18), 155 (60), 151 (100); IR (neat) 3386, 2950, 2871, 1467, 1377, 1215, 1147, 1028, 911 cm^{-1}; UV (95% EtOH) λ_{max} 262, 252 (sh) nm. **1f**: ^{1}H NMR ($CDCl_3$) δ 0.51 (3 H, s), 0.88 (3 H, t, J = 7.3 Hz), 0.93 (3 H, d, J = 6.8 Hz), 1.22 (6 H, s), 3.93 (1 H, tt, J = 9.1 and 4.3 Hz), 4.99 and 5.32 (each 1 H, d, J = 1.5 Hz), 5.97 and 6.34 (each 1 H, d, J = 11 Hz); MS m/z 472 (M^+, 1), 454 (13), 436 (5), 415 (9), 397 (5), 379 (4), 361 (2), 307 (4), 155 (22), 151 (100); IR (neat) 3380, 2948, 2869, 1595, 1464, 1377, 1128, 1049, 911 cm^{-1}; UV (95% EtOH) 263 nm.

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Supplementary Material Available: ^{1}H NMR spectra of compounds **3**, **5**, **6a**, **7**, **11**, **12**, **14**, **15**, **16a**, **16b**, **1b**, **1c**, **1d**, **1e**, and **1f** and the X-ray structure of **12** (17 pages). This material is contained in libraries on microfiche, immediately follows this articles in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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