Calcitriol Derivatives with Two Different Side Chains at C-20. II. Diastereoselective Syntheses of the Metabolically Produced 24(*R*)-Hydroxygemini[1]

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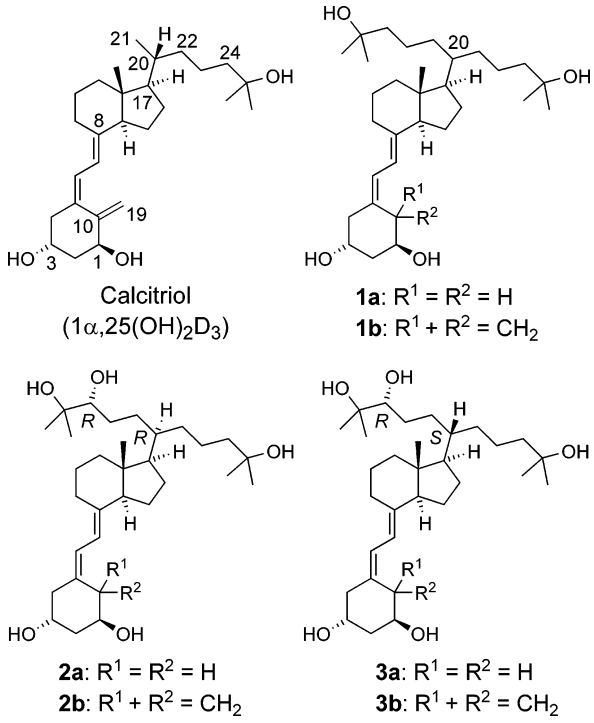
Vitamin D derivatives containing two side chains emanating at C-20 are known as gemini. We have recently synthesized two gemini which are related to calcitriol and 19-norcalcitriol containing two identical side chains. The metabolism of these species involves 24(*R*)-hydroxylation on one of the side chains. To determine the outcome of this diastereospecific transformation, we synthesized both C-20 epimeric pairs containing the 24(*R*)-hydroxy group in the gemini and 19-norgemini series. On the basis of the availability of these reference compounds, it was shown that the metabolic hydroxylation occurred at the *pro-R* side chain in both gemini compounds. In comparison to the parent compounds, the 24-hydroxygemini required higher doses to increase blood calcium levels in mice and to suppress INF-γ release in MLR.

1. Introduction

The calcitriol derivatives **1a** and **1b** featuring two identical side chains emanating at C-20 exert the full spectrum of calcitriol activities such as binding to the VDR, suppression of increased parathyroid hormone levels in nephrectomized rats, INF-γ release in MLR cells, stimulation of HL-60 leukemia cell differentiation, and inhibition of solid-tumor cell proliferation.[2−4] The major metabolic conversion of calcitriol (1α,25(OH)$_2$D$_3$) proceeds through a series of side-chain modifications to the biologically inactive calcitroic acid. This cascade is initiated by the 24*R*-hydroxylase leading to 1α,24(*R*),25(OH)$_3$D$_3$, followed by 24-oxidation, 23-hydroxylation, and oxidative chain cleavage at C23/24 leading to calcitroic acid.[5−8] Similar to the introduction of a double bond at C-16, epimerization at C-20 can arrest the degradative sequence at the 24-oxo level.[7] This phenomenon moved gemini **1a** and **1b** to the focal point of interest by raising several questions as the two calcitriol side chains at C-20 in gemini mimic the presence of both calcitriol C-20 epimers in one molecule. Would gemini, similar to calcitriol, also be monohydroxylated? In other words, would the inherent presence of the "20-epi-feature" also arrest the metabolic degradation at the 24-oxo stage followed by initial 24-hydroxylation? Would the hydroxylation produce a 24(*R*)-metabolite? Most importantly, which of the two side chains would be subject to metabolism as indicated by initial hydroxylation? And, would the regio- and stereospecificity of the hydroxylation remain invariant to changes in the A-ring?



2. Metabolic Studies and Preliminary Pharmacological Results

Metabolism in bone cells and in perfused rat kidney converted **1a** and **1b** each to a single 24-hydroxy species. A 24(*R*)-hydroxylation creates a new stereocenter at C-20 and thus the possibility of two side-chain hydroxylated epimers of the 24(*R*),20(*R*)- and 24(*R*),20(*S*)-configurations as shown in **2a**, **2b** and **3a**, **3b**, respectively. Synthetic access to these species, as described herein, allowed the determination as to which of the two side chains in **1a** and **1b** are the preferred metabolic substrates, and the evaluation of their potential as pharmaceutically useful entities.

Calcitriol (1α,25(OH)$_2$D$_3$) was shown by rat kidney perfusion[9−11] to be rapidly metabolized to calcitroic acid.

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Table 1. Calcium Levels (mg/dL) with Standard Errors (SE) after Four Diurnal Drug Administrations

drug	vehicle (miglyol)	drug concentrations (mg/kg) 0.3	1	3	10	30	100	MTD (mg/kg)
1a	9.33 (0.08)			10.00 (0.19)	12.50 (0.72)	16.50 (0.07)		3
2a			9.63 (0.08)	9.37 (0.08)	9.57 (0.15)	9.77 (0.22)	10.77 (0.08)	30
3a			9.53 (0.23)	9.90 (0.19)	9.43 0.08)	9.43 (0.16)	9.57 (0.15)	>100
1b	9.80 (0.07)		11.07 (0.25)	12.30 (0.44)	16.73 (0.80)			<1
2b		9.60 (0.12)	9.70 (0.07)	9.73 (0.11)				3
3b		9.80 (0.07)	9.73 (0.11)	9.63 (0.15)				3

More than 50% of the substrate disappeared from the kidney perfusate due to its rapid metabolism mediated by the C-24-oxidation pathway. The gemini compounds **1a** and **1b**, on the other hand, were metabolically more stable as only about 20% of the substrate disappeared from the kidney perfusate. Moreover, only one polar metabolite each was detected in the perfusates, apparently resisting further degradation. The chemospecificity to produce a single metabolite from each gemini was confirmed by chromatography and mass spectrometry and the regiospecificity at the C24 site by periodate-mediated glycol cleavage. The same 24-hydroxy metabolites were also produced in rat osteosarcoma cells (UMR 106). Considering the heterotopic environment of the two identical side chains in **1a** and **1b**, metabolic mono-24-hydroxylation can potentially occur either on their *pro-R* or *pro-S* side chain. More specifically, hydroxylation of the *pro-R* chain in **1b**, as shown in **2b**, is tantamount to hydroxylation of the chain with the natural configuration. At first glance, one could therefore speculate that the *pro-R* chain should be the preferred substrate, thus identifying **2a** and **2b** as the more likely metabolic products of **1a** and **1b**. On the other hand, the observation that 20-epicalcitriol is hydroxylated at a higher rate than its natural 20(*R*) counterpart might suggest selective hydroxylation at the unnatural side chain thus rendering **3a** and **3b** as the more likely metabolic prospects. A comparison of each epimeric pair with the corresponding metabolic products has now indeed revealed the natural *pro-R* side chain as the exclusive metabolic substrate. Figure 1 illustrates the identification of the major metabolic product of **1b** as **2b** by comparison of its HPLC profile with those of the synthetic specimens **2b** and **3b**. These studies were repeated with **1a** as substrate. The major metabolite was again compared with **2a** and **3a** and unambiguously identified as **2a**. More specifically, the substrates **1a** and **1b** were eluted from the HPLC column at 21.4 and 18.6 min, respectively, and produced but one major metabolite each upon incubation with osteosarcoma sells (UMR 106) that eluted at 37.5 and 30.9 min, respectively. These elution times are congruent with the ones exhibited by the 20*R* isomers **2a** and **2b** and deviant from the times of 32.9 and 27.7 min, characteristic of the 20*S* isomers **3a** and **3b**, respectively.

Table 1 shows the minimum tolerated dose (μg/kg) in mice based on calcium levels (mg/dL) after 4 diurnal drug administrations. In general, the 19-norgemini **1a**, **2a**, and **3a** were better tolerated than the counterparts containing the "natural" A-ring (i.e., the 3,5-dihydroxy-2-methylenecyclohexylidene ring of calcitriol). No increase in calcium levels was observed when **3a** was administered to mice at a dose as high as 100 μg/kg. These comparisons corroborate DeLuca's discovery of diminished hypercalcemic activity of compounds containing the 19-nor feature.[12] Concomitant with this improved tolerance, correspondingly higher doses were required to inhibit INF-γ release in MLR as shown in Table 2. Regardless of the A-ring constitution, hydroxylation at the *pro-R* side chain increases the required dose for INF-γ release inhibition by a factor of ca. 20; an equivalent change at the *pro-S* side chain, however, necessitates a ca. 100-fold increase. A comparison with calcitriol confirms that 24-hydroxylation in the series of compounds containing the natural A-ring increases the required dose for INF-γ release inhibition less drastically than those in the 19-nor category.

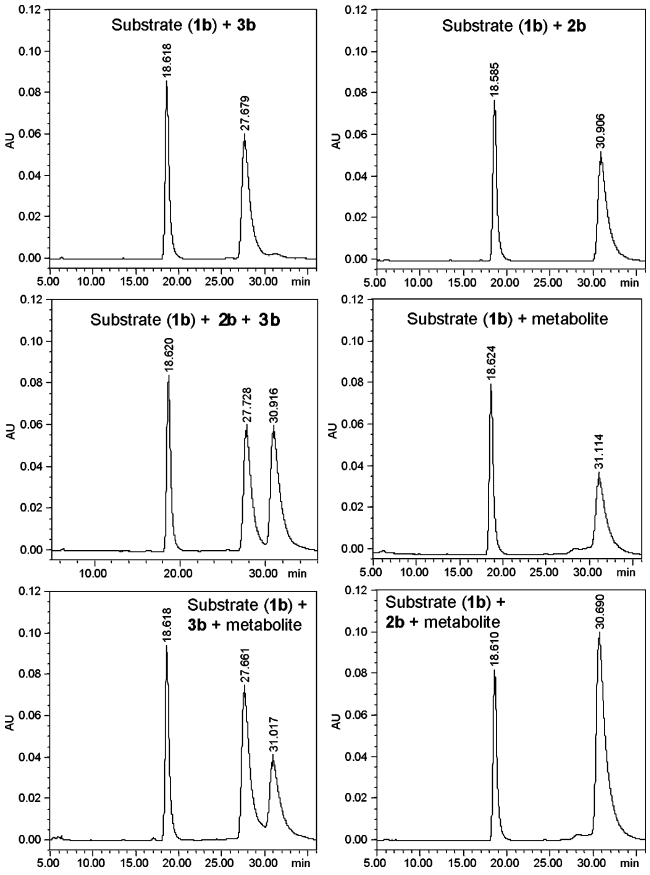


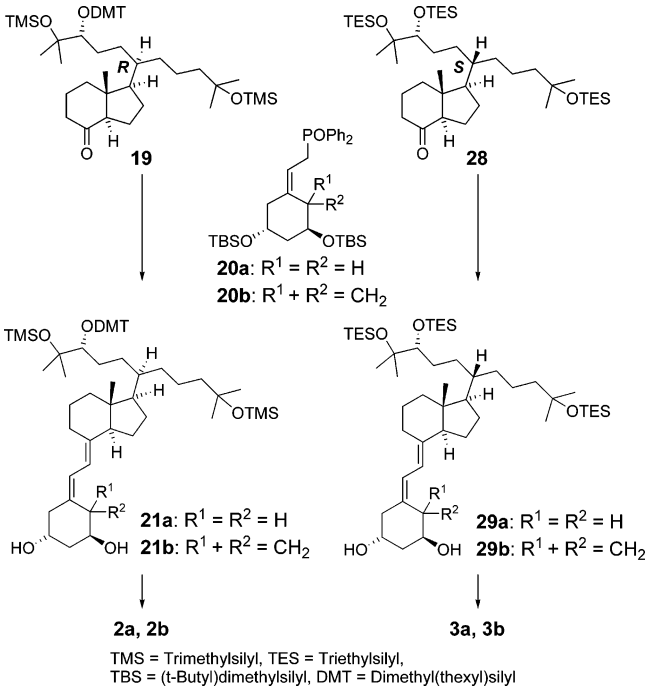
Figure 1. HPLC comparisons of the metabolite derived from **1b** with the 20(*R*) and 20(*S*) epimers **2b** and **3b**, respectively.

Table 2. IC_{50} Values for INF-γ Release in MLR

drug characteristic		drug	MLR IFN-γ IC_{50} (pM) drug (D)[a]	drug/calcitriol
19-nor		**1a**	44 (8)	1.8
	20(*R*)	**2a**	781 (254)	31
	20(*S*)	**3a**	3856 (2800)	160
natural A-ring		**1b**	4 (1)	0.1
	20(*R*)	**2b**	80 (17)	2.5
	20(*S*)	**3b**	579 (4)	18

[a] D = average error, N = 3.

Scheme 1



3. Synthetic Methods[13]

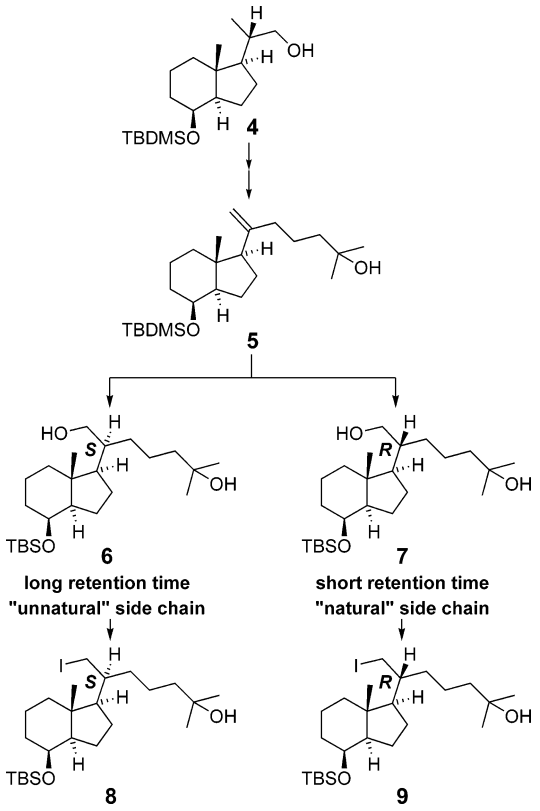
For the synthesis of the two epimeric pairs **2a**, **3a** and **2b**, **3b** we chose the convergent and established Wittig–Horner reaction employing the Lythgoe phosphine oxide coupling protocol[14–16] in which the two elaborated ketones **19** and **28** are each linked to **20a** and **20b** as illustrated in Scheme 1. A single step removed all five silyl protecting groups in each member of the pairs **21a**, **21b** and **29a**, **29b** and led to the target compounds **2a**, **2b** and **3a**, **3b**. The different protective groups in **19** and **28** are the result of two dissimilar pathways investigated for their synthesis.

We have previously described two different desymmetrization processes of the gemini side chains.[17,18] One of them, pertinent to the current synthetic task, and diagrammatically represented in Scheme 2, provides the pair of epimeric iodoalkenes **8** and **9**. Their synthesis commenced with the 4-*O*-(*tert*-butyldimethylsilyl)-Lythgoe diol **4** that was first converted to alkenol **5**. A subsequent hydroboration furnished the epimeric pair of diols **6** and **7**, easily separated by chromatography and transformed to the iodides **8** and **9**, respectively.

The assignment of absolute configuration of **6** and **7** rests on a crystallographic analysis of a derivative of **7**.[18] Consequently, diol **7** with the "natural" side chain, corresponding to the 20(*R*) designation in the vitamin D nomenclature, exhibits the shorter retention time on a silica gel column than its epimeric counterpart **6**.

The syntheses of the pairs **2a**, **2b** and **3a**, **3b** were achieved by two different routes as indicated in Scheme 1. The sequence of steps leading to **2a** and **2b** involves an elaborate functional-group protection strategy, previously established,[19] with the aim to ensure the integrity of the *trans*-octahydroindene ring juncture. This sequence, illustrated in Scheme 3 for the synthesis of **2a** and **2b**, commenced with the conversion of diol **6**[18] to the iodo alcohol **8** followed by iodide displacement with sodium benzenesulfinate. The resulting alcohol **10a** was silylated to afford **10b** and then lithiated and treated

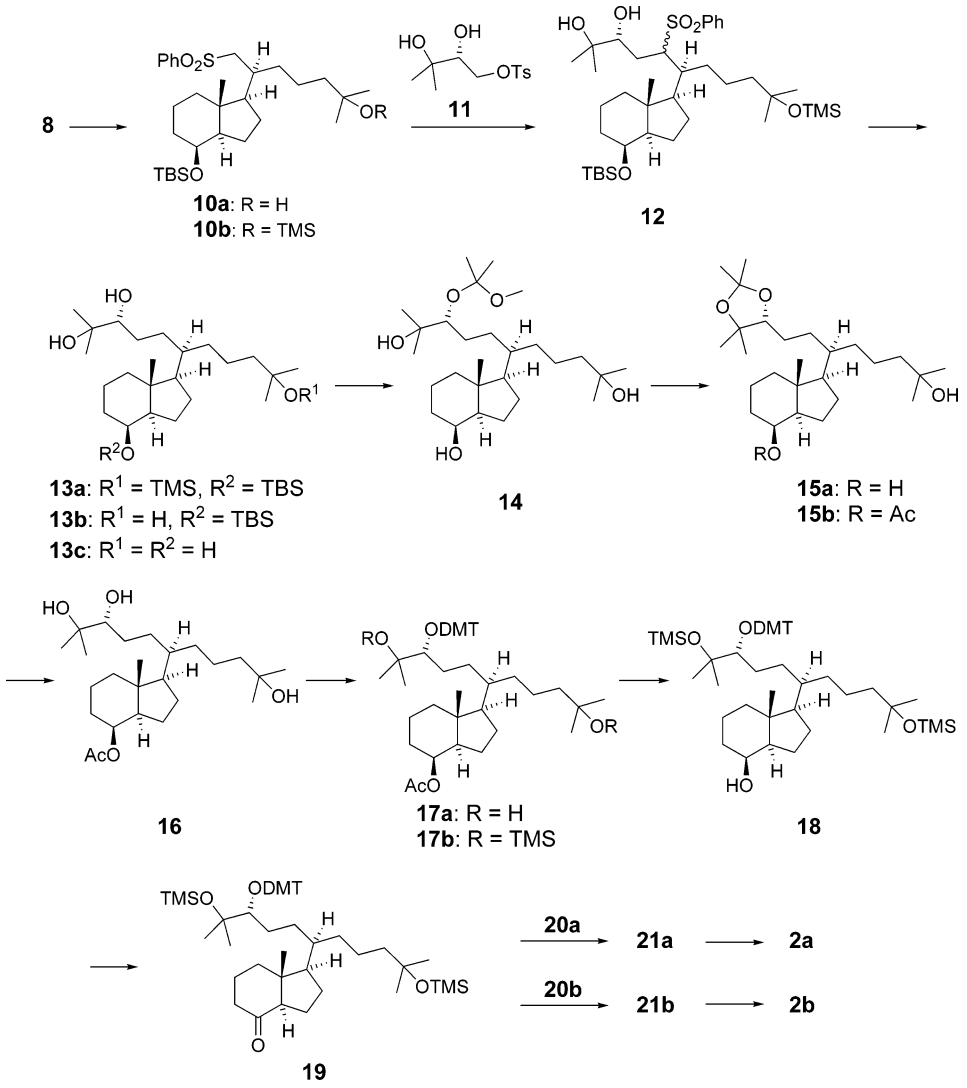
Scheme 2



with the 2-oxiranyl-2-propanol, prepared in situ from **11**, leading to the epimeric diol mixture **12**.

A subsequent reductive desulfonylation gave **13a** but also some partially desilylated **13b**. Rather than completely desilylating this mixture to obtain the tetraol **13c** directly, we opted for the selective removal of the trimethylsilyl group providing **13b** as a crystalline intermediate and hence the opportunity for additional purification and characterization. A subsequent treatment with fluorosilicic acid then produced the tetraol **13c**. Treatment of **13c** with acetone and 2,2-dimethoxypropane with pyridinium tosylate as catalyst gave a mixture of **15a** and a more polar material, assumed to be the acetal **14**. Somewhat surprisingly, it was a brief *aqueous* treatment of this mixture that converted this more polar substance quantitatively to **15a**. A subsequent reaction with acetic anhydride in pyridine led to the *O*-acetyl compound **15b**, and 80% aqueous acetic acid at 68 °C hydrolyzed the acetal moiety within 2.5 h to produce **16**. In an attempt to balance product stability with the ease of final removal of the five silyl ethers, as present in the projected condensation product **21b**, we introduced just one bulky silyl ether moiety and employed trimethylsilyl ether protection for the two tertiary hydroxyl groups. Indeed, O-silylation with thexyldimethylsilyl chloride proceeded regioselectively to **17a**, and a following treatment with 1-(trimethylsilyl)imidazole gave **17b**. The 4-acetoxy group was then removed by treatment with lithium aluminum hydride, and the resulting alcohol **18** was oxidized to the ketone **19** using pyridinium dichromate. The standard coupling protocol, employing **20a** and **20b** as Wittig–Horner components, gave **21a** and **21b**, respectively, and single treatments with tetrabutylammonium fluoride furnished the target compounds **2a** and **2b**.

Scheme 3

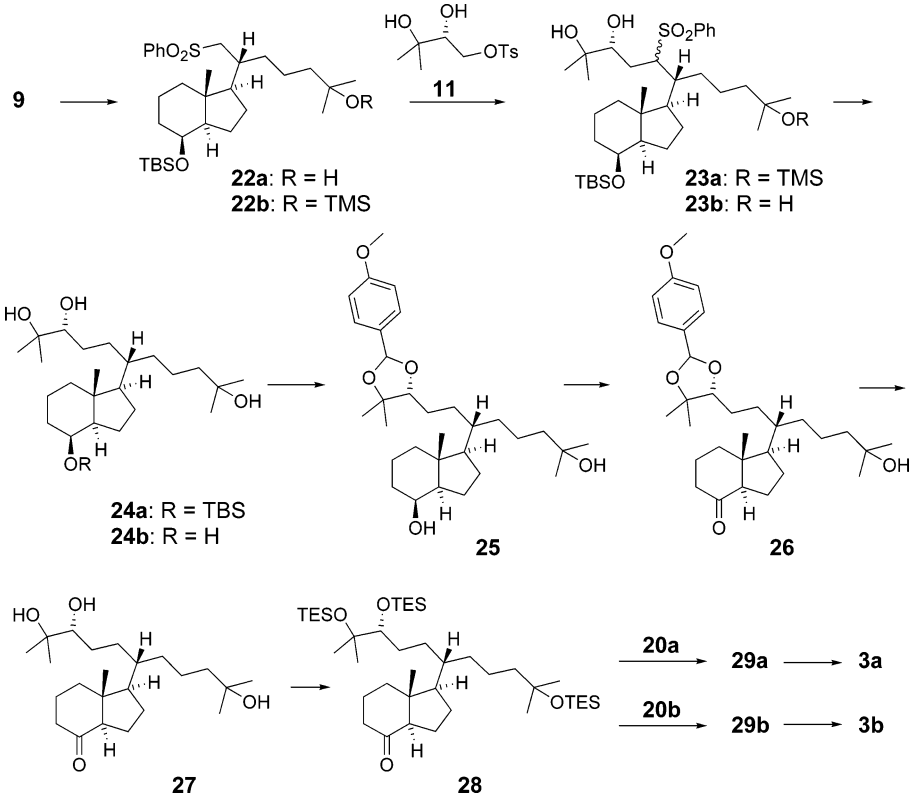


For the syntheses of **3a** and **3b** we designed shorter routes as shown in Scheme 4. The conversion of diol **7** to **23a** via the iodo alcohol **9**, phenyl sulfone **22a**, trimethylsilyl derivative **22b**, and subsequent condensation of **22b** with **11** was conducted in a fashion very similar to the corresponding steps described previously for the other epimer. The trimethylsilyl group in the epimeric pair **23a**, however, was now removed prior to reductive desulfonylation thereby avoiding a mixture of mono- and disilylated species as observed in the form of **13a** and **13b** in the course of synthesis of the other epimer. Thus, treating **23a** with methanolic oxalic acid gave **23b**, and stirring of this triol with sodium amalgam led to **24a**. A subsequent treatment with fluorosilicic acid in acetonitrile served for the generation of the tetraol **24b**. In a major deviation from the former synthetic pathway, **24b** was treated with 4-methoxybenzylidene dimethyl acetal and pyridinium tosylate to produce the oxolane **25**, which was oxidized with pyridinium dichromate to ketone **26**. A considerable synthetic improvement was thus realized as the 4-methoxybenzylidene acetal proved to be sufficiently acid labile to permit its hydrolysis under conditions that did not compromise the trans ring juncture of the 7a-methyloctahydro-4-indenone system. A subsequent treatment with either 80% acetic acid or 1 N methanolic oxalic acid, the latter previously employed for the selective hydrolysis of the tertiary trimethylsilyl ether function in both **13a** and **23a**, converted **26** to the ketotriol **27**, which was treated with chlorotriethylsilane in *N*,*N*-dimethylformamide and imidazole to produce rapidly the disilyl ether. Further reaction of the second tertiary alcohol proceeded smoothly overnight, leading to **28**, which was condensed with **20a** and **20b** leading to **29a** and **29b**, respectively. One deprotection step with tetrabutylammonium fluoride liberated all five protected hydroxyl groups in each of the two pentasilyl ethers to furnish, after chromatographic purification, compounds **3a** and **3b**.

4. Experimental Section

All operations involving vitamin D analogues were conducted in amber-colored glassware in a nitrogen atmosphere. Tetrahydrofuran was distilled from sodium−benzophenone ketyl just prior to its use, and solutions of solutes were dried with sodium sulfate. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Optical rotations were measured at 25 °C. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ unless indicated otherwise. UV spectra were recorded using methanol as solvent. TLC was carried out on silica gel plates (Merck F-254) with visualization under short-wavelength UV light or by spraying the plates with 5% phosphomolybdic acid in methanol followed

Scheme 4



by heating. Flash chromatography was carried out on 40−65 μm mesh silica gel. Preparative HPLC was performed on a 5 × 50 cm column and 15−30 μm mesh silica gel at a flow rate of 100 mL/min. HPLC for metabolic studies was carried out on a Zorbax Sil column, 9.4 × 250 mm using 15% 2-propanol in hexane as isocratic mobile phase at a flow rate of 2 mL/min. Quoted retention times refer to this system.

6(*S*)-7-Benzenesulfonyl-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-2-methylheptan-2-ol (10a). A mixture of **8** (0.94 g, 1.8 mmol), sodium benzenesulfinate (2.18 g, 13 mmol), and *N*,*N*-dimethylformamide (31.8 g) was stirred at room temperature for 12 h and then in a 40 °C bath for ca. 6 h until all educt was converted as shown by TLC (1:4 ethyl acetate−hexane). The solution was equilibrated with 1:1 ethyl acetate−hexane (120 mL) and 1:1 brine−water (45 mL). The organic layer was washed with water (4 × 25 mL) and brine (10 mL), then dried, and evaporated to leave a colorless oil, 1.0317 g. This material was flash chromatographed using a stepwise gradient (1:9, 1:6, and 1:3 ethyl acetate−hexane) to give **10a** as a colorless oil, 0.930 g, 96%: 300 MHz ^{1}H NMR δ −0.02 (3H, s), 0.00 (3H, s), 0.87 (9H, s), 0.88 (3H, s), 1.12 (1H, m), 1.20 (6H, s), 1.2−1.8 (18H, m), 1.81 (1H, m), 3.09 (2H, m), 3.97 (1H, brs), 7.59 (3H, m), 7.91 2H, m). Anal. ($C_{30}H_{52}O_4SSi$) C, H.

(1*R*,3a*R*,4*S*,7a*R*)-1-((*S*)-1-Benzenesulfonylmethyl-5-methyl-5-trimethylsilanyloxyhexyl)-4-(*tert*-butyldimethylsilanyloxy)-7a-methyloctahydroindene (10b). 1-(Trimethylsilyl)imidazole (1 mL) was added to a solution of **10a** (0.800 g) in cyclohexane (10 mL), stirred overnight, and then flash chromatographed using a stepwise gradient of hexane and 1:39 and 1:19 ethyl acetate−hexane. The elution was monitored by TLC (1:4 ethyl acetate−hexane) leading to **10b** as a colorless syrup, 0.792 g, 87%: 300 MHz ^{1}H NMR δ 0.00 (3H, s), 0.02 (3H, s), 0.12 (9H, s), 0.90 (9 + 3H, s), 1.16 (1H, m), 1.20 (6H, s), 1.2−1.6 (15H, m), 1.66−1.86 (3H, m), 3.10 (2H, m), 4.00 (1H, brs), 7.56−7.70 (3H, m), 7.93 (2H, m).

(1*R*,3*R*,6*R*)-6-[(3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-2,10-dimethylundecane-2,3,10-triol (13b). A solution of **10b** (0.7513 g, 1.23 mmol) and diol **11** (0.508 g, 1.85 mmol) in tetrahydrofuran (28 mL) was cooled to −35 °C, and then 2.5 M butyllithium in hexane (2.75 mL) was added dropwise. The temperature was allowed to rise to −20 °C and maintained at that temperature for 6 h. Reaction progress was monitored by TLC (1:4 ethyl acetate−hexane) exhibiting the educt (R_f 0.71) and the two epimeric diols **12** (R_f 0.09 and 0.12). Toward the end of the reaction period the temperature was increased briefly to 0 °C and lowered again to −10 °C, and then saturated ammonium chloride (25 mL) was added followed by ethyl acetate (50 mL) and enough water to dissolve the precipitated salts. The resulting aqueous phase was extracted with ethyl acetate (15 mL). The combined extracts were washed with brine (15 mL), dried, and evaporated. The resulting syrup was flash chromatographed using a stepwise gradient of 1:9, 1:6, 1:4, and 1:1 ethyl acetate−hexane to give **12** as a colorless syrup, 0.8586 g. This material was dissolved in a mixture of tetrahydrofuran (30 mL) and methanol (18 mL), then 5% sodium amalgam (20 g) was added. The reductive desulfonylation was complete after stirring of the mixture for 14 h. Progress of the reaction was monitored by TLC (1:1 ethyl acetate−hexane), which showed the disappearance of the epimeric **12** (R_f 0.63 and 0.74) and the generation of **13a** (R_f 0.79) and the partially desilylated analogue **13b** (R_f 0.16). The mixture was diluted with methanol (20 mL) and stirred for 3 min, then ice (20 g) was added, the mixture was stirred for 2 min, and the supernatant was decanted into a mixture containing saturated ammonium chloride (50 mL). The residue was repeatedly washed with small amounts of tetrahydrofuran, which was also added to the salt solution, which was then equilibrated with ethyl acetate (80 mL). The aqueous layer was re-extracted once with ethyl acetate (20 mL), and the combined extracts were washed with brine (10 mL), then dried, and evaporated. The resulting colorless oil, containing both **13a** and **13b**, was dissolved in 10 mL of a 1 N oxalic acid solution in methanol (prepared from oxalic acid dihydrate), effecting the selective hydrolysis of the trimethylsilyl ether within minutes. Calcium carbonate (1 g) was added and the suspension stirred overnight and then filtered. The filtrate was evaporated and the resulting residue flash chromatographed using a stepwise gradient of 1:4, 1:2, 1:1, and 2:1 ethyl acetate−hexane, giving a residue of the triol **13b** that crystallized in very fine branching needles from acetonitrile, 0.45 g: mp 94−95 °C; $[\alpha]_D$ +44.1° (methanol, *c* =

0.37); ^{1}H NMR δ −0.005 (3H, s), 0.007 (3H, s), 0.89 (9H, s), 0.92 (3H, s), 1.15 (1H, m), 1.16 (3H, s), 1.21 (9H, s), 1.2−1.6 (19H, m), 1.67 (1H, m), 1.79 (2H, m), 1.90 (2H, m), 2.06 (1H, m), 3.31 (1H, brd, J = 10 Hz), 4.00 (1H, brs); LR-ES(−) *m/z* 533 (M + Cl), 497 (M − H); HR-ES(+) calcd for $C_{29}H_{58}O_4Si$ + Na 521.3996, found 521.4003. Anal. ($C_{29}H_{58}O_4Si$) C, H.

(1*R*,3*R*,6*R*)-6-((3a*R*,4*S*,7a*R*)-4-Hydroxy-7a-methyloctahydroinden-1-yl)-2,10-dimethylundecane-2,3,10-triol (13c). A stirred solution of the triol **13b** (0.4626 g, 0.927 mmol) in acetonitrile (10 mL) and dioxane (0.7 mL) was cooled to 10 °C, and a fluorosilicic acid solution[18] (2 mL) was added dropwise. The cooling bath was removed and the 2-phase system further diluted with acetonitrile (2 mL) and then stirred at room temperature for 3^1/$_4$ h. The disappearance of educt was monitored by TLC (ethyl acetate). The mixture was equilibrated with water (10 mL) and ethyl acetate (30 mL). The aqueous phase was re-extracted with ethyl acetate (2 × 20 mL), and the combined extracts were washed consecutively with water (5 mL), brine (10 mL), and 1:1 brine−saturated sodium hydrogen carbonate solution and then dried. The residue was purified by flash chromatography using a stepwise gradient from 1:1 to 2:1 ethyl acetate−hexane and neat ethyl acetate to give a residue, which was taken up in 1:1 dichloromethane−hexane, filtered, and evaporated to furnish **13c** as amorphous solids, 0.3039 g (85%): $[\alpha]_D$ +42.6° (methanol, c = 0.48); ^{1}H NMR (DMSO-d_6) δ 0.87 (3H, s), 0.97 (3H, s), 1.02 (3H, s), 1.04 (6H, s), 1.1−1.4 (18H, m), 1.5−1.8 (4H, m), 1.84 (1H, m), 2.99 (1H, dd, J = 6 and 10 Hz), 3.87 (1H, brs), 4.02 (1H, s, OH), 4.05 (1H, s, OH), 4.16 (1H, d, OH, J = 3.6 Hz), 4.20 (1H, d, OH, J = 6.4 Hz); LR-ES(+) *m/z* 384 (M), 383 (M − H); HR-ES(+) calcd for (M + Na) 407.3132, found 407.3134.

(1*R*,3a*R*,4*S*,7a*R*)-1-{(*R*)-5-Hydroxy-5-methyl-1-[2-((*R*)-2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)ethyl]hexyl}-7a-methyloctahydroinden-4-ol (15a). A solution of the tetraol **13c** (0.2966 g, 0.771 mmol) and pyridinium tosylate (100 mg) in acetone (8 mL) and 2,2-dimethoxypropane (8 mL) was kept at room temperature for 12 h. TLC analysis (ethyl acetate) showed the absence of educt (R_f 0.21) and two new spots with R_f 0.82 and 0.71, the former the expected **15a** and the latter assumed to be the methyl acetal **14**. The reaction mixture was diluted with water (5 mL) and stirred for 10 min. At that time only the spot with the higher R_f value was observed. The mixture was neutralized with sodium hydrogen carbonate (0.5 g) and then equilibrated with ethyl acetate (50 mL) and brine (5 mL). The organic layer was washed with water (5 mL) and brine (5 mL), then dried, and evaporated to leave **15a** as a sticky residue (0.324 g), which was used directly in the next step; 300 MHz ^{1}H NMR δ 0.94 (3H, s), 1.10 (3H, s), 1.20 (1H, m), 1.22 (6H, s), 1.25 (3H, s), 1.34 (3H, s), 1.41 (3H, s), 1.2−1.65 (20H, m), 1.78−1.86 (3H, m), 1.93 (1H, m), 3.62 (1H, dd, J = 4.6 and 8.3 Hz), 4.08 (1H, brs).

Acetic Acid (1*R*,3a*R*,4*S*,7a*R*)-1-{(*R*)-5-Hydroxy-5-methyl-1-[2-((*R*)-2,2,5,5-tetramethyl-[1,3]dioxolan-4-yl)ethyl]-hexyl}-7a-methyloctahydroinden-4-yl Ester (15b). The residue obtained above was dissolved in pyridine (6.9 g) and further diluted with acetic anhydride (3.41 g). The mixture was allowed to stand at room temperature for 24 h and then in a 35 °C bath for ca. 10 h until the educt was no longer detectable (TLC, ethyl acetate). The mixture was diluted with toluene and evaporated. The residue was purified by flash chromatography (1:4 ethyl acetate−hexane) to give **15b** as colorless syrup, 0.3452 g, 97%: ^{1}H NMR δ 0.89 (3H, s), 1.10 (3H, s), 1.20 (1H, m), 1.22 (6H, s), 1.25 (3H, s), 1.33 (3H, s), 1.41 (3H, s), 1.25−1.6 (19H, m), 1.72 (1H, m), 1.82 (2H, m), 1.95 (1H, m), 2.05 (3H, s), 3.63 (1H, dd, J = 4.4 and 8.4 Hz), 5.15 (1H, brs); LR-FAB(+) *m/z* 467 (M + H), 465 (M − H), 451 (M − Me).

Acetic Acid (1*R*,3a*R*,4*S*,7a*R*)-1-[(1*R*,4*R*)-4,5-Dihydroxy-1-(4-hydroxy-4-methylpentyl)-5-methylhexyl]-7a-methyloctahydroinden-4-yl Ester (16). A solution of **15b** (0.334 g, 0.716 mmol) in 80% acetic acid (2 mL) was kept in a 68 °C bath. TLC (ethyl acetate, R_f 0.33) monitored the progress of the hydrolysis. The educt was no longer detectable after 2.5 h. The mixture was evaporated and then coevaporated with a small amount of toluene to leave **16** as a colorless film (0.303 g), which was used directly in the next step: 300 MHz ^{1}H NMR δ 0.89 (3H, s), 1.17 (3H, s), 1.22 (6H, s), 1.56 (3H, s), 1.1−1.6 (21H, m), 1.6−2.0 (5H, m), 2.04 (3H, s), 3.32 (1H, brd, J = 10 Hz), 5.15 (1H, brs). A small amount was further purified by flash chromatography (2:1 ethyl acetate−hexane). Anal. ($C_{25}H_{46}O_5$) C, H.

Acetic Acid (1*R*,3a*R*,4*S*,7a*R*)-1-[(1*R*,4*R*)-4-[Dimethyl-(1,1,2-trimethyl-propyl)silanyloxy]-5-hydroxy-1-(4-hydroxy-4-methylpentyl)-5-methylhexyl]-7a-methyloctahydroinden-4-yl Ester (17a). A solution of the triol **16** (0.30 g), imidazole (0.68 g, 10 mmol) and dimethylthexylsilyl chloride (1.34 g, 7.5 mmol) in *N*,*N*-dimethylformamide (6 g) was kept at room temperature. After 48 h 4-(*N*,*N*-dimethylamino)-pyridine (15 mg) was added and the mixture stirred for an additional 24 h. Reaction progress was monitored by TLC (ethyl acetate; **16**, R_f 0.83; **17a**, R_f 0.38). The mixture was diluted with water (2 mL), stirred for 10 min, and then distributed between ethyl acetate (45 mL) and water (20 mL). The aqueous layer was extracted once with ethyl acetate (10 mL). The combined organic phases were washed with water (4 × 12 mL) and brine (8 mL), then dried, and evaporated. The residual oil was purified by flash chromatography using a stepwise gradient of 1:9 and 1:4 ethyl acetate−hexane to give **17a** as colorless syrup. A small amount of unreacted educt (80 mg) was eluted with ethyl acetate. The syrupy **17a** was used directly in the next step: ^{1}H NMR δ 0.13 (3H, s), 0.14 (3H, s), 0.87 (6H, s), 0.91 (9H, m), 1.10 (1H, m), 1.14 (3H, s), 1.15 (3H, s), 1.21 (6H, s), 1.1−1.6 (19H, m), 1.6−1.9 (5H, m), 1.94 (1H, brd, J = 12.8 Hz), 2.05 (3H, s), 3.38 (1H, brs), 5.15 (1H, brs).

Acetic Acid (1*R*,3a*R*,4*S*,7a*R*)-1-[(1*R*,4*R*)-4-[Dimethyl-(1,1,2-trimethylpropyl)silanyloxy]-5-methyl-1-(4-methyl-4-(trimethylsilanyloxy)pentyl)-5-(trimethylsilanyloxy)-hexyl]-7a-methyloctahydroinden-4-yl Ester (17b). 1-(Trimethylsilyl)imidazole (0.90 mL, 6.1 mmol) was added to a solution of **17a** (0.2929 mg) in cyclohexane (6 mL), and the mixture was stirred for 12 h and then flash chromatographed (1:79 ethyl acetate−hexane) to yield **17b** as a colorless syrup (0.3372 g): ^{1}H NMR δ 0.074 (3H, s), 0.096 (3H, s), 0.103 (9H, s), 0.106 (9H, s), 0.82 (1H, m), 0.83 (6H, s), 0.88 (6 + 3H, m), 1.32 (3H, s), 1.20 (12H, s), 1.15−1.6 (14H, m), 1.6−1.9 (5H, m), 1.97 (1H, brd, J = 12.8 Hz), 2.05 (3H, s), 3.27 (1H, m), 5.15 (1H, brs); LR-FAB(+) *m/z* 712 (M), 711 (M − H), 697 (M − Me), 653 (M − AcO), 627 (M − C_6H_{13}).

(1*R*,3a*R*,4*S*,7a*R*)-1-[(1*R*,4*R*)-4-[Dimethyl-(1,1,2-trimethylpropyl) silanyloxy]-5-methyl-1-(4-methyl-4-(trimethylsilanyloxy)pentyl)-5-(trimethylsilanyloxy)hexyl]-7a-methyloctahydroinden-4-ol (18). A stirred solution of **17b** (0.335 mg, 0.47 mmol) in tetrahydrofuran (15 mL) was cooled in an ice bath, and a 1 M solution of lithium aluminum hydride in tetrahydrofuran (2 mL) was added dropwise. TLC (1:9 ethyl acetate−hexane) showed complete conversion of **17b** (R_f 0.61) to **18** (R_f 0.29) after 1.5 h. A 2 M sodium hydroxide solution (14 drops) was added, followed by water (0.5 mL) and ethyl acetate (30 mL). A small amount of Celite was added, and, after stirring for 15 min, the liquid layer was decanted off. The solid residue was rinsed repeatedly with ethyl acetate, and the combined liquid phases were evaporated to leave a colorless syrup, which was taken up in hexane, filtered, and evaporated to yield **18** (0.335 g), which was used without further purification: ^{1}H NMR δ 0.075 (3H, s), 0.10 (21H, brs), 0.82 (1H, m), 0.84 (6H, s), 0.89 (6H, m), 0.93 (3H, s), 1.13 (3H, s), 1.20 (9H, s), 1.2−1.6 (16H, m), 1.6−1.7 (2H, m), 1.82 (3H, m), 1.95 (1H, brd, J = 12.4 Hz), 3.27 (1H, m), 4.08 (1H, brs); LR-FAB(+) *m/z* 585 (M − C_6H_{13}), 481 (M − TMSO); HR-ES(+) calcd for $C_{37}H_{78}O_4Si_3$ + Na 693.5100, found 693.5100.

(1*R*,3a*R*,7a*R*)-1-[(1*R*,4*R*)-4-[Dimethyl-(1,1,2-trimethylpropyl)silanyloxy]-5-methyl-1-(4-methyl-4-(trimethylsilanyloxy)pentyl)-5-(trimethylsilanyloxy)hexyl]-7a-methyloctahydroinden-4-one (19). Celite (0.6 g) was added to a stirred solution of **18** (0.310 g, 0.462 mmol) in dichloromethane (14 mL) followed by pyridinium dichromate (0.700 g, 1.86 mmol). TLC (1:4 ethyl acetate−hexane) monitored the conversion of **18** (R_f 0.54) to the ketone **19** (R_f 0.76). The

mixture was diluted with cyclohexane after 4.5 h and then filtered through a layer of silica gel. Filtrate and ether washes were combined and evaporated. The residue was flash chromatographed (1:39 ethyl acetate−hexane) to give **19** as a colorless syrup, 0.2988 g, 96.6%: ^{1}H NMR δ 0.078 (3H, s), 0.097 (3H, s), 0.107 (18H, s), 0.64 (3H, s), 0.81 (1H, m), 0.84 (6H, s), 0.89 (6H, m), 1.134 (3H, s), 1.201 (3H, s), 1.207 (3H, s), 1.211 (3H, s), 1.3−1.6 (14H, m), 1.6−1.7 (3H, m), 1.88 (1H, m), 2.04 (2H, m), 2.2−2.32 (2H, m), 2.46 (1H, dd, J = 7.5 and 11.5 Hz), 3.28 (1H, m); LR-FAB(+) *m/z* 583 (M − C_6H_{13}), 479 (M − OTMS); HR-ES(+) calcd for $C_{37}H_{76}O_4Si_3$ + Na 691.4943, found 691.4949.

(1*R*,3a*S*,7a*R*)-4-[2-[(3*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilanyloxy)-2-methylenecyclohex-(*Z*)-ylidene]-eth-(*E*)-ylidene]-7a-methyl-1-[5-methyl-1(*R*)-[4-methyl-4-(trimethylsilanyloxy)pentyl]-4(*R*)-[dimethyl(1,1,2-trimethylpropyl)silanyloxy]-5-trimethylsilanyloxyhexyl]octahydroindene (21b). A solution of 2.5 M butyllithium in hexane (0.17 mL) was added dropwise to a solution of (1*S*,5*R*)-1,5-bis-((*tert*-butyldimethyl)silanyloxy)-3-[2-(diphenylphosphinoyl)-eth-(*Z*)-ylidene]-2-methylene-cyclohexane (**20b**, 0.1415 g, 0.396 mmol) in tetrahydrofuran (2 mL) at −70 °C. After 10 min a solution of ketone **19** (0.1415 g, 0.211 mmol) in tetrahydrofuran (2 mL) was added dropwise over a 15 min period. The reaction was quenched after 4 h by the addition of pH 7 phosphate buffer (1 M, 2 mL). The temperature was allowed to increase to 0 °C, and then hexane (30 mL) was added. The aqueous layer was re-extracted with hexane (15 mL). The combined extracts were washed with brine (5 mL), dried, and evaporated to give a colorless oil, which was purified by flash chromatography (1:100 ethyl acetate−hexane) to yield **21b** as colorless syrup, 0.173 g, 79%: ^{1}H NMR δ 0.068 (15H, m), 0.103 (12H, s), 0.107 (9H, s), 0.53 (3H, s), 0.82 (1H, m), 0.84 (6H, s), 0.88 (18H, m), 0.89 (6H, m), 1.14 (3H, m), 1.20 (9H, s), 1.2−1.9 (22H, m), 1.97 (2H, m), 2.22 (1H, dd, J = 7.5 an 13 Hz), 2.45 (1H, brd, J = 13 Hz), 2.83 (1H, brd, J = 13 Hz), 3.28 (1H, m), 4.20 (1H, m), 4.38 (1H, m), 4.87 (1H, d, J = 2 Hz), 5.18 (1H, d, J = 2 Hz), 6.02 (1H, d, J = 11.4 Hz, 6.24 (1H, d, J = 11.4 Hz); LR-FAB(+) *m/z* 1033 (M + H), 1032 (M), 1031 (M − H), 901 (M − TBDMS).

(3*R*,6*R*)-6-{(1*R*,3a*S*,7a*R*)-4-[2-((*R*)-3-(*S*)-Hydroxy-5-hydroxy-2-methylene-cyclohexylidene)-(*E*)-ethylidene]-7a-methyloctahydroinden-1-yl}-2,10-dimethylundecane-2,3,-10-triol (2b). The pentasilyl ether **21b** (0.153 g, 0.148 mmol), as obtained in the previous experiment, was dissolved in a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (3.5 mL). TLC (ethyl acetate) monitored reaction progress. The solution was diluted with brine (5 mL) after 24 h, stirred for 5 min, and then equilibrated with ethyl acetate (35 mL) and water (15 mL). The aqueous layer was re-extracted once with ethyl acetate (15 mL). The combined organic layers were washed with water (5 × 10 mL) and once with brine (5 mL), then dried, and evaporated. The residue was purified by flash chromatography using a stepwise gradient of ethyl acetate and 1:100 methanol−ethyl acetate, furnishing **2b** as colorless, microcrystalline material from methyl formate−pentane, 70 mg, 91%, HPLC 30.9 min: $[\alpha]_D$ +34.4° (methanol, c = 0.51); UV_{max} (ϵ) 213 (13554), 265 (16029), 241 (s, 12801) nm; ^{1}H NMR δ 0.55 (3H, s), 1.17 (3H, s), 1.22 (9H, s), 1.15−1.8 (22H, m), 1.8−2.1 (7H, m), 2.32 (1H, dd, J = 6.6 and 13.6 Hz), 2.61 (1H, d), 2.84 (1H, brd), 3.32 (1H, brs), 4.23 (1H, brs), 4.43 (1H, brs), 5.01 (1H, s), 5.33 (1H, s), 6.03 (1H, d, J = 11.4 Hz), 6.38 (1H, d, J = 11.4 Hz); LR-ES(+) *m/z* 519 (M + H), 501 (M − H); HR-ES(+) calcd for $C_{32}H_{54}O_5$ + Na 541.3863, found 541.3870. Anal. ($C_{32}H_{54}O_5$) C, H.

(3*R*,6*R*)-6-{(1*R*,3a*S*,7a*R*)-4-[2-((*R*)-3-(*R*)-Hydroxy-5-hydroxy-cyclohexylidene)-(*E*)-ethylidene]-7a-methyloctahydroinden-1-yl}-2,10-dimethylundecane-2,3,10-triol (2a). The condensation of ketone **19** with (1*R*,3*R*)-1,3-bis-((*tert*-butyldimethyl)silanyloxy)-5-[2-(diphenylphosphinoyl)ethylidene]-cyclohexane (**20a**) and the deprotection of the resulting **21a** (83 mg) was conducted as described for **21b**, with the exception that the exposure to tetrabutylammonium fluoride was extended to 48 h, to furnish **2a**, purified by flash chromatography with a stepwise gradient using 4:1 ethyl acetate−hexane, ethyl acetate, and ethyl acetate containing 1.5% methanol, and obtained as a colorless, microcrystalline material from methyl formate−pentane, 38.4 mg (93%): HPLC 37.5 min; TLC R_f 0.05 (ethyl acetate); $[\alpha]_D$ +66.5° (methanol, c = 0.37); UV_{max} (ϵ) 243 (32317), 251 (38040), 261 (25777) nm; ^{1}H NMR δ 0.55 (3H, s), 1.17 (3H, s), 1.22 (9H, s), 1.24−1.60 (23H, m), 1.60−1.70 (1H, m), 1.71−2.08 (5H, m), 2.18−2.24 (2H, m), 2.46−2.50 (1H, m), 2.72−2.83 (2H, m), 3.32 (1H, brd), 4.05 (1H, brs), 4.12 (1H, brs), 5.86 (1H, d, J = 11.2 Hz), 6.31 (1H, d, J = 11.2 Hz); LR-ES(+) *m/z* 529 (M + Na); LR-ES(−) *m/z* 541 (M + Cl); HR-ES(+) calcd for $C_{31}H_{54}O_5$ + Na 529.3863, found 529.3869. Anal. ($C_{31}H_{54}O_5$) C, H.

(*R*)-7-Benzenesulfonyl-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-2-methylheptan-2-ol (22a). A solution of **9**[18] and sodium benzenesulfinate (0.263 g, 1.6 mmol) in *N*,*N*-dimethylformamide (5 mL) was stirred in a 77 °C bath for 3 h. The solution was equilibrated with 1:1 ethyl acetate−hexane (25 mL) and the organic layer washed with water (5 × 10 mL), dried, and evaporated. The residue was flash chromatographed with a stepwise gradient of 1:9, 1:4, and 1:3 ethyl acetate−hexane to furnish the sulfone as a colorless syrup: ^{1}H NMR δ −0.02 (3H, s), 0.005 (3H, s), 0.79 (3H, s), 0.87 (9H, s), 1.12 (1H, m), 1.19 (6H, s), 1.12 (1H, m), 1.20 (6H, s), 1.2−1.8 (18H, m), 2.08 (1H, m), 3.09 (1H, dd, J = 9.3 and 14.5 Hz), 3.31 (1H, dd, J = 3 and 14.5 Hz), 3.97 (1H, brs), 7.58 (3H, m), 7.66 (1H, m), 7.91 2H, m); LR-ES(+) *m/z* 600 (M + Na + MeCN), 559 (M + Na); LR-ES(−) *m/z* 536 (M), 535 (M − H); HR-ES(+) calcd for $C_{30}H_{52}O_4SSi$ + Na 559.3248, found 559.3253.

(1*R*,3a*R*,4*S*,7a*R*)-1-((*R*)-1-Benzenesulfonylmethyl-5-methyl-5-(trimethylsilanyloxy)hexyl)-4-(*tert*-butyldimethylsilanyloxy)-7a-methyloctahydroindene (22b). 1-(Trimethylsilyl)imidazole (0.146 mL) was added to a solution of **22a** (0.145 g, 0.27 mmol) in cyclohexane (2 mL). After 17 h the product was purified by flash chromatography using a stepwise gradient of 1:79 and 1:39 ethyl acetate−hexane to give **22b** as a colorless residue, 0.157 g: TLC (1:9 ethyl acetate−hexane) R_f 0.14; 300 MHz ^{1}H NMR δ −0.02 (3H, s), 0.00 (3H, s), 0.87 (12H, s), 1.12 (1H, m), 1.17 (6H, s), 1.2−1.6 (15H, m), 1.6−1.9 (3H, m), 3.08 (2H, m), 3.97 (1H, brs), 7.53−7.70 (3H, m), 7.90 (2H, d, J = 7 Hz).

(6*R*,5ξ,3*R*)-5-Benzenesulfonyl-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-2,10-dimethyl-10-(trimethylsilanyloxy)undecane-2,3-diol (23a). A solution of **22b** (0.2589, 0.425 mmol) and diol **11** (0.176 g, 0.638 mmol) in tetrahydrofuran (9 mL) was cooled to −25 °C, and 1.6 M butyllithium in hexane (1.4 mL) was added. The temperature was raised to −20 °C, maintained at that temperature for 3 h, and then maintained at −10 °C for 2.5 h and at 0 °C for 10 min. The mixture was cooled again to −10 °C, saturated ammonium chloride solution (5 mL) was added, and then the mixture was equilibrated with ethyl acetate (50 mL) and enough water to dissolve precipitated salts. The aqueous layer was re-extracted with ethyl acetate (15 mL), the combined extracts were dried and evaporated, and the residue was purified by flash chromatography using a stepwise gradient of 1:6, 1:4, and 1:1 ethyl acetate−hexane to produce the diastereomeric mixture **23a** as a colorless syrup, 0.212 g, 70%: 300 MHz ^{1}H NMR δ 0.00 (3H, s), 0.017 (3H, s), 0.12 (9H, s), 0.81 (3H, s), 0.89 (9H, s), 1.16 (1H, m), 1.19 (12H, m), 1.1−1.6 (20H, m), 1.6−1.8 (2H, m), 3.10 (1H, dd, J = 8.4 and 14.7 Hz), 3.30 (1H, m), 3.99 (1H, brs), 7.61 (2H, m), 7.67 (1H, m), 7.93 (2H, m).

(3*R*,6*S*)-6-[(1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilanyloxy)-7a-methyloctahydroinden-1-yl]-2,10-(dimethyl)-undecane-2,3,10-triol (24a). The mixture represented by **23a** (0.186 mg, 0.262 mmol) was dissolved in 0.5 M oxalic acid dihydrate in methanol (2.5 mL). The solution was stirred for 15 min, then calcium carbonate was added (0.5 g), and the suspension was stirred overnight and then filtered. The filtrate was evaporated to give the diastereomeric mixture **23b** as a white foam, 0.188 g, 98%: TLC R_f 0.06 (1:1 ethyl acetate−hexane). This material was combined with a second lot (0.426 g, 0.667 mmol) and dissolved in a mixture of tetrahydrofuran

(15 mL) and methanol (9 mL). Then sodium amalgam (5% sodium, 10.8 g) was added, and the suspension was stirred for 24 h. The reaction progress was monitored by TLC (1:1 ethyl acetate−hexane) to observe the production of **24a** (R_f 0.17). The mixture was diluted with methanol (3 mL), stirred for 5 min, then further diluted with water (10 mL), stirred for 2 min, and decanted into a saturated ammonium chloride solution (25 mL). The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed with pH 7 phosphate buffer (5 mL) and then brine (10 mL), dried, and evaporated. The residue was purified by flash chromatography using a stepwise gradient of 1:1 and 2:1 ethyl acetate−hexane to provide **24a** as a colorless syrup, 0.244 g, 73%: ^{1}H NMR δ −0.006 (3H, s), 0.006 (3H, s), 0.86 (9H, s), 0.92 (3H, s), 1.11 (1H, m), 1.15 (3H, s), 1.21 (9H, s), 1.2−1.75 (21H, m), 1.7−1.85 (3H, m), 1.90 (1H, m), 3.29 (1H, brd), 3.99 (1H, brs); LR-ES(+) *m/z* 521 (M + Na), 481 (M − OH); LR-ES(−) *m/z* 544 (M + CH_2O_2), 543 (M − H + CH_2O_2), 533 (M − Cl); HR-ES(+) *m/z* calcd for $C_{29}H_{58}O_4Si$ + Na 521.3996, found 521.3999.

(3*R*,6*S*)-6-((1*R*,3a*R*,4*S*,7a*R*)-4-Hydroxy-7a-methyloctahydroinden-1-yl)-2,10-(dimethyl)undecane-2,3,10-triol (24b). An aqueous fluorosilicic acid solution (3 mL) was added to a stirred solution of **24a** (0.240 g, 0.481 mmol) in acetonitrile (12 mL). TLC (ethyl acetate) monitored the reaction. After 2.5 h compound **24b** (R_f 0.37) was the predominating species, produced at the expense of less polar **24a**. The mixture was equilibrated with ethyl acetate and water (10 mL), the aqueous layer was re-extracted with water (2 × 10 mL), and the combined extracts were washed with water (6 mL) and brine (2 × 10 mL) and then dried and evaporated. The colorless residue was flash chromatographed using a stepwise gradient of 1:2, 1:1, and 2:1 ethyl acetate−hexane to elute some unreacted **24a**, followed by **24b**, obtained as a colorless syrup, 0.147 g, 79%: ^{1}H NMR δ 0.94 (3H, s), 1.12 (1H, m), 1.15 (3H, s), 1.21 (9H, s), 1.15−1.7 (20H, m), 1.7−1.9 (5H, m), 1.96 (1H, brd), 3.29 (1H, d, J = 9.6 Hz), 4.08 (1H, brs); LR-ES(+) *m/z* 448 (M + Na + MeCN), 407 (M + Na); LR-ES(−) *m/z* 419 (M + Cl); HR-ES(+) calcd for $C_{23}H_{44}O_4$ + Na 407.3132, found 407.3135.

(1*R*,3a*R*,4*S*,7a*R*)-1-((*S*)-5-Hydroxy-1-{2-[(*R*)-2-(4-methoxyphenyl)-5,5-dimethyl-[1,3]dioxolan-4-yl]ethyl}-5-methylhexyl)-7a-methyloctahydroinden-4-ol (25). 4-Methoxybenzaldehyde dimethyl acetal (60 μL, 0.35 mmol) was added to a solution of **24b** (81.2 mg, 0.211 mmol) in dichloromethane (2 mL), followed by a solution (0.2 mL) containing pyridinium tosylate (200 mg) in dichloromethane (10 mL). Reaction progress was followed by TLC (1:2 ethyl acetate−hexane), which showed 4-methoxybenzaldehyde dimethyl acetal (R_f 0.80), 4-methoxybenzaldehyde (R_f 0.65), educt **24b** (R_f 0.42), and product **25** (R_f 0.26). After 5^3/$_4$ h the mixture was stirred for 15 min with saturated sodium hydrogencarbonate solution (5 mL) and then equilibrated with ethyl acetate (25 mL). The organic layer was washed with brine (5 mL), dried, and evaporated. The residue was flash chromatographed using a stepwise gradient of 1:3 and 1:2 ethyl acetate−hexane to yield **25** as a colorless syrup, 0.106 mg (100%): ^{1}H NMR δ 0.94 (3H, s), 1.19 (3H, s), 1.21 (3H, s), 1.23, 1.35 and 1.24, 1.37 (6H, s each, major and minor 5,5-dimethyloxolane diastereomer), 1.1−1.7 (18H, m), 1.7−1.9 (5H, m), 1.9−2.0 (2H, m), 3.65 (1H, m), 3.81 (3H, s), 4.08 (1H, brs), 5.78 and 5.96 (1H, s each, major and minor acetal diastereomer), 6.89 (2H, m), 7.41 (2H, m).

(1*R*,3a*R*,7a*R*)-1-((*S*)-5-Hydroxy-1-{2-[(*R*)-2-(4-methoxyphenyl)-5,5-dimethyl-[1,3]dioxolan-4-yl]ethyl}-5-methylhexyl)-7a-methyloctahydroinden-4-one (26). Pyridinium dichromate (230 mg, 0.61 mmol) was added to a stirred mixture containing **25** (0.0838, 0.167 mmol), Celite (185 mg), and dichloromethane (4 mL). The conversion of **25** (R_f 0.31) to **26** (R_f 0.42) was monitored by TLC (1:25 methanol−chloroform). The mixture was diluted with dichloromethane (10 mL) after 2.5 h and then filtered through a layer of silica gel. Filtrate and washings (1:1 dichloromethane−ethyl acetate) were evaporated, and the residue was chromatographed (1:4 ethyl acetate−hexane) to give ketone **26**, 0.0763 g, 91%: ^{1}H NMR δ 0.63 (3H, s), 1.19, 1.21 and 1.23 (6H, s each, Me_2COH), 1.25, 1.36, 1.38 (6H, m,s,s, 5,5-dimethyloxolane diastereomer), 1.1−1.9 (18H, m), 1.9−2.1 (3H, m), 2.1−2.4 (2H, m), 2.45 (1H, m), 3.66 (1H, m), 3.802 and 3.805 (3H, s each), 5.78 and 5.95 (1H, s each, major and minor acetal diastereomer), 6.89 (2H, m), 7.39 (2H, m).

(1*R*,3a*R*,7a*R*)-1-[(1*S*,4*R*)-4,5-Dihydroxy-1-(4-hydroxy-4-methylpentyl)-5-methylhexyl]-7a-methyloctahydroinden-4-one (27). The ketone **26** was stirred in a 1 N oxalic acid solution in 90% methanol. The mixture became homogeneous after a few minutes. TLC (ethyl acetate) suggested complete reaction after 75 min (R_f 0.24 for **27**). Thus, calcium carbonate (0.60 g) was added and the suspension stirred overnight and then filtered. The filtrate was evaporated and flash chromatographed using a stepwise gradient of 4:1:5 dichloromethane−ethyl acetate−hexane, 1:1 ethyl acetate−hexane, and neat ethyl acetate, to produce **27** as a colorless residue, 0.060 mg, 94%: ^{1}H NMR δ 0.5 (3H, s), 1.17 (3H, s), 1.22 (6H, s), 1.23 (3H, s), 1.2−1.21 (23H, m), 2.15−2.35 (2H, m), 2.45 (1H, dd, J = 7 and 11 Hz), 3.30, 1H, brd); LR-ES(+) *m/z* 424.5 (M + H + MeCN), 406.4 (M + H + Na); 383.5 (M + H); HR-ES(+) calcd for $C_{23}H_{42}O_4$ + Na 405.2975, found 405.2979.

(1*R*,3a*R*,7a*R*)-7a-Methyl-1-[(1*S*,4*R*)-5-methyl-1-(4-methyl-4-(triethylsilanyloxy)pentyl)-4,5-bis-(triethylsilanyloxy)hexyl]octahydroinden-4-one (28). A mixture of **27** (0.055 g, 0.143 mmol), imidazole, (14.9 mg, 1.69 mmol), *N*,*N*-dimethylpyridine (6 mg), triethylchlorosilane (0.168 mL, 1 mmol), and *N*,*N*-dimethylformamide (1.5 mL) was stirred for 17 h. The reaction was followed by TLC (1:4 ethyl acetate−hexane) and showed rapid conversion to the disilyl intermediate (R_f 0.47). Further reaction proceeded smoothly overnight to give the fully silylated **28** (R_f 0.90). The solution was equilibrated with water (3 mL), and ethyl acetate (20 mL). The ethyl acetate layer was washed with water (3 × 4 mL), dried, and evaporated. The residue was flash chromatographed using a stepwise gradient of hexane and 1:100 ethyl acetate−hexane to yield **28** as a colorless syrup, 0.0813 g, 78.4%: ^{1}H NMR δ 0.55−0.64 (21H, m), 0.92−0.97 (27H, m), 1.12 (3H, s), 1.18 (3H, s), 1.19 (3H, s), 1.21 (3H, s), 1.1−1.7 (18H, m), 1.9−2.15 (2H, m), 2.15−2.35 (2H, m), 2.43 (1H, dd, J = 7.7 and 11 Hz), 3.30 (1H, dd, J = 3 and 8.4 Hz).

(1*R*,3a*S*,7a*R*)-4(*E*)-{2-[(*R*)-3-((*R*)-(*tert*-Butyldimethylsilanyloxy))-5-(*tert*-butyldimethylsilanyloxy)-cyclohexylidene]ethylidene}-7a-methyl-1-[(1*S*,4*R*)-5-methyl-1-(4-methyl-4-(triethylsilanyloxy)pentyl)-4,5-bis-(triethylsilanyloxy)-hexyl]octahydroindene (29b). A solution of 1.6 M butyllithium in hexane (0.14 mL) was added to a solution of **20b** (0.1308 g, 0.224 mmol) in tetrahydrofuran (1.5 mL) at −70 °C. After 10 min a solution of ketone **28** (0.0813 g, 0.112 mmol) in tetrahydrofuran (1.5 mL) was added dropwise over a 15 min period. The ylide color had faded after 3 h, thus pH 7 phosphate buffer (2 mL) was added and the temperature allowed to increase to 0 °C. The mixture was equilibrated with hexane (30 mL), and the organic layer was washed with brine (5 mL), dried, and evaporated to give a colorless oil, which was purified by flash chromatography (1:100 ethyl acetate−hexane). No attempt was made to recover unreacted **28** as only the band with R_f 0.33 (TLC 1:39 ethyl acetate−hexane) was collected. Evaporation of those fractions gave **29b** as a colorless syrup, 0.070 g, 57%: ^{1}H NMR δ 0.06 (12H, brs), 0.53−0.64 (21H, m), 0.88 (18H, s), 0.92−0.97 (27H, m), 1.11 (3H, s), 1.177 (3H, s), 1.184 (3H, s), 1.195 (3H, s), 1−1.9 (22H, m), 1.98 (2H, m), 2.22 (1H, m), 2.45 (1H, m), 2.83 (1H, brd, J = 13 Hz, 3.27 (1H, d, J = 6 Hz), 4.19 (1H, m), 4.38 (1H, m), 4.87 (1H, brs), 5.18 (1H, brs), 6.02 (1H, d, J = 11 Hz), 6.24 (1H, d, J = 11 Hz).

(3*R*,6*S*)-6-{(1*R*,3a*S*,7a*R*)-4(*E*)-[2-((*R*)-3-(*R*)-Hydroxy-5-hydroxy-cyclohexylidene)-(*E*)-ethylidene]-7a-methyl-octahydroinden-1-yl}-2,10-dimethylundecane-2,3,10-triol (3b). The deprotection reaction of **29b** (0.068 g, 0.062 mmol) in a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.5 mL), monitored by TLC (R_f 0.18, ethyl acetate), gradually proceeded over a 24 h period to give **3b**. The mixture was diluted with brine (5 mL), stirred for 5 min, and then

equilibrated with ethyl acetate (35 mL) and water (15 mL). The aqueous layer was re-extracted once with ethyl acetate (35 mL), and the combined extracts were washed with water (5 × 10 mL) and brine (5 mL), then dried, and evaporated. The residue was flash chromatographed using a linear gradient of 1:1 and 2:1 ethyl acetate−hexane and 2:98 methanol−ethyl acetate to give a residue, which was taken up in methyl formate and evaporated to give **3b** as a white foam, 30 mg, 93%; HPLC 27.7 min; $[\alpha]_D$ +29.3° (methanol, $c = 0.34$); UV_{max} (ϵ) 211 (15017), 265 (15850), 204 (s, 14127), 245 (s, 13747) nm; ^{1}H NMR δ 0.55 (3H, s), 1.16 (3H, s), 1.21 (9H, s), 1.2−1.75 (22H, m), 1.75−188 (2H, m), 188.-2.05 (5H, m), 2.31 (1H, dd, $J = 6.8$ and 13.4 Hz), 2.60 (1H, d), 2.84 (1H, brd), 3.30 (1H, brd), 4.42 (1H, m), 4.31 (1H, brs), 5.00 (1H, s), 5.33 (1H, s), 6.01 (1H, d, $J = 11.2$ Hz), 6.37 (1H, d, $J = 11.2$ Hz); LR-ES(+) m/z 564 (M + H_2CO_2); 563 (M − H + H_2CO_2); HR-ES(+) calcd for $C_{32}H_{54}O_5$ + Na 541.3863, found 541.3854. Anal. ($C_{32}H_{54}O_5$) C, H.

(3*R*,6*S*)-6-{(1*R*,3a*S*,7a*R*)-4(*E*)-[2-((*R*)-3-(*S*)-Hydroxy-5-hydroxy-2-methylene-cyclohexylidene)-(*E*)-ethylidene]-7a-methyloctahydroinden-1-yl}-2,10-dimethylundecane-2,3,10-triol (3a). The condensation of ketone **28** (0.109 g, 0.15 mmol) was repeated with **20a** (0.1729 g, 0.30 mmol), to give **29a** (0.142 g, 88%). This pentasilyl ether (0.118 g) was deprotected as described for **29b**, but extending the contact time with the tetrabutylammonium fluoride solution to 48 h, to furnish **3a** in microcrystalline form (0.0479 g, 86%): HPLC 32.9 min; $[\alpha]_D$ +71.3° (methanol, $c = 0.32$); UV_{max} (ϵ) 243 (32679), 251(38564), 261(26095), 225 (s, 12097), 235 (s, 22062) nm, ^{1}H NMR δ 0.55 (3H, s), 1.17 (3H, s), 1.22 (9H, s), 1.10−1.75 (22H, m), 1.75−1.9 (4H, m), 1.9−2.1 (3H, m), 2.18−2.25 (2H, m), 2.47−2.49 (1H, m), 2.73−2.83 (2H, m), 3.32 (1H, m), 4.04 (1H, brs), 4.12 (1H, brs), 5.86 (1H, d, $J = 11.4$ Hz), 6.31 (1H, d, $J = 11.4$ Hz; LR-ES(−) m/z 552 (M + H_2CO_2), 551 (M − H + H_2CO_2), HR-ES(+) calcd for $C_{31}H_{54}O_5$ + Na 529.3863, found 529.3865. Anal. ($C_{31}H_{54}O_5$), C, H.

Supporting Information Available: Elemental analysis data for **2a**,**b**, **3a**,**b**, **10a**, **13b**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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