Synthesis of (-)-Calicoferol B

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The first total synthesis of (-)-calicoferol B (III) is described. The cyclozirconation product 1, prepared in enantiomerically pure form, was converted into the CD ring chiron II. This was coupled with the aromatic A-ring, and then the side chain was constructed with control of relative and absolute configuration to complete the total synthesis of III. The first total synthesis of (-)-calicoferol B (1) is described. The cyclozirconation product 8, prepared in enantiomerically pure form, was converted into the CD ring chiron 6. This was coupled with the aromatic A-ring, and then the side chain was constructed with control of relative and absolute configuration to complete the total synthesis of 1.

Introduction

Osteopontin (OPN) is one of the major noncollagenous bone matrix proteins produced by osteoblasts and osteoclasts.1 Substrate-bound OPN promotes attachment of osteoclasts,2 whereas soluble OPN can alter calcium levels in osteoclasts.3 These observations suggest that OPN may play a key role both in cell attachment and in controlling subsequent bone cell functions such as resorption. Indeed, it has been observed that OPN knockout mice are resistant to ovariectomy-induced bone resorption.4 This suggests that induced downregulation of OPN may be an effective strategy for the clinical treatment of osteoporosis.

We had been intrigued by the structural similarity between calicoferol B (1), astrogorgiadiol (2), and 1α,25-dihydroxyvitamin D₃ ("calcitriol", 3), the active hormonal form of vitamin D.5 We recently completed the total synthesis of astrogorgiadiol (2),5 a secosterol isolated from a Japanese marine sponge of the genus Astrogorgia,7 and submitted the synthetic material for screening. Astrogorgiadiol (2) was inactive in most of the 1α,25-dihydroxy-vitamin D₃ assays. Astrogorgiadiol (2) did, however, show remarkable activity in one of them, clearly downregulating the production of osteopontin at 30 nM concentration in cell culture.8 In contrast, 1α,25-dihydroxyvitamin D₃ (3) and its other known derivatives dramatically upregulate osteopontin production.9

The synthetic route to astrogorgiadiol (2) that we had established6 was efficient, but it was not flexible. We have therefore developed an entirely new route (Scheme 1) to this class of vitamin D-like materials. This triply convergent approach allows ready modification of A-ring, D-ring, and side-chain substitution. It was particularly intriguing that semiempirical calculations suggested that the two geometric isomers of 4 should be of approximately equal energy. If this proved to be true, it would be possible to prepare either relative configuration of the side chain from the same precursor. We have taken as our first objective the preparation of calicoferol B (1), a...
marine secosterol isolated from the gorgonian Calicogorgia sp. in 1991 that showed lethality to brine shrimp with an LD$_{50}$ of 2.3 ppm.  

Results and Discussion

The key to this approach was the preparation of the bicyclic chiron 6 (Scheme 1). We had already established that cyclozirconation/carbonylation of the diene 9 proceeded smoothly to give the crystalline ketone 8.  

The immediate task was to differentiate (Scheme 2) the two methylenes flanking the ketone at C(16) (steroid numbering). We expected that the C(15) methylene, being sterically less congested, would be kinetically more acidic than the C(17) methylene. Indeed, exposure of ketone 8 to LDA at $-78^\circ$C followed by reaction with ethyl chloroformate gave preponderantly the keto ester 7.  

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Carrying out this same transformation at $-100^\circ$C gave an even higher 10/7 ratio. In contrast, exposure of ketone 8 to diethyl carbonate in the presence of NaH and a catalytic amount of ethanol in DME gave a 2:1 ratio of the desired keto ester 7 to its regioisomer 10. The keto esters 10 and 7 could be easily identified by their $^1$H NMR spectra. The H(15) signal in keto ester 7 was a doublet with an 13.0 Hz coupling constant at $\delta$ 3.04, whereas the H(17) signal in keto ester 7 was a singlet at $\delta$ 2.83. The undesired keto ester 10 could be efficiently recycled to the tetracyclic ketone 8.

Protection (Scheme 3) of the ketone carbonyl group in the desired keto ester 7 with ethylene glycol in the presence of triethyl orthoformate and a catalytic amount of p-TsOH-H$_2$O produced the ketal 12, accompanied by an uncharacterized mixture. This mixture was further treated with p-TsOH-H$_2$O in ETOH to give an additional portion of ketal 12 as well as the dial ketal 11. Further protection then converted the dial ketal 11 to the desired ketal 12. Selected benzenesulfonation of the primary alcohol in 12 yielded the monobenzenesulfonate 13, which was reduced with DiBAL-H to furnish the bicyclic chiron 6. The transformation of the ketone 8 (Scheme 2) to the monobenzenesulfonate 6 proceeded in 59% overall yield.

The aromatic A-ring synthon 5 was prepared from the commercially available 3-methylanisole (14) (Scheme 4). Thus, bromination and benzenesulfonylation of 14 following the procedure of Hoye gave the bromo sulfone 15. We had originally thought to prepare 5 by direct methylation of 15, but CH$_3$MgBr with Cu or Ni catalysts returned only unreacted starting material. The alternative replacement of the bromine with copper(I) cyanide

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proceeded efficiently, to yield the nitrile 16. Reduction with DIABAL-H to the aldehyde 17 followed by Wolff-Kishner reduction furnished the aromatic A-ring synthons 5.

Coupling of the bicyclic chiron 6 with the aromatic A-ring synthons 5 gave the sulfonyl 18 (Scheme 5). Desulfonation of 18 with Na and ethanol in THF produced the diol 19, which was oxidized with Dess–Martin periodinane to afford the keto aldehyde 20. Addition of isohexylmagnesium bromide followed by hydrolysis and dehydration gave the easily separable enones 4 and 21 in the predicted 1:1 ratio. The two enones could readily be identified by their 1H NMR spectra. The H(20) signal of 4 appeared at δ 5.76, whereas the H(20) signal of 21 appeared at δ 6.53. Either enone could be equilibrated efficiently to the ~1:1 mixture by treatment with KI in acetic acid.

Based on the literature precedent, we expected that conjugate addition of lithium dimethyl cuprate to enones 4 and 21 would proceed from the α-face. Thus, addition to the desired enone 4 would give the (natural) C(20α) methyl, while addition to the enone 21 would give the epimeric C(20β) methyl. Indeed, conjugate addition of lithium dimethyl cuprate to enone 4 (Scheme 6) gave the dione 22. Reduction of the dione 22 with L-Selectride afforded the diol 23, which was demethylated with triethylsilane in the presence of a catalytic amount of tris(pentafluorophenyl)boron followed by desilylation with TBAF to provide the target molecule, (−)-calicoferol B.

(21) Semiempirical calculations (MOPAC PM3) had shown that ii is preferred over i by a 1.81 kcal/mol, so i should be the predominant product. In contrast, iii and iv had only a 0.01 kcal/mol difference, suggesting a ~1:1 ratio at equilibrium.

Scheme 3

Scheme 4

Scheme 5

SCHEME 3

SCHEME 4

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not 26 each other, demonstrating the stereochemical homogeneity of 22 and of 24. The identity of the synthetic 1 (and not 26) with the natural product was established by 13C NMR. The C(21) and C(22) signals of synthetic 1 appeared at δ 18.9 (lit. 18.51) and δ 36.9 (lit. 36.59), respectively, whereas the corresponding C(21) and C(22) signals of 26 appeared at δ 19.3 and 35.5.

Conclusion

The first total synthesis of (−)-calicoferol B (1) has been accomplished. We believe that the triply convergent synthetic strategy described here will offer a general route to the naturally occurring A-ring aromatic B-seco steroids.

**Experimental Procedures**

**General Methods.** 1H NMR (400 MHz) and 13C NMR (100 MHz) spectra were obtained as solutions in deuteriochloroform (CDCl3) unless otherwise noted. 13C multiplicities were determined with the aid of a J REGT pulse sequence, differentiating the signals for methyl and methine carbons as “down” from methylene and quaternary carbons as “up”. The infrared (IR) spectra were determined as neat oils. Optical rotations were determined as solutions in chloroform unless otherwise noted. R\(_\text{f}\) values indicated refer to thin-layer chromatography (TLC) on 25 x 10 cm, 250 μm analytical plates coated with silica gel GF and developed in the solvent system indicated. Silica gel (60 Å) was used for flash column chromatography. 

Tetrahydrofuran (THF) and diethyl ether were distilled from calcium hydride under dry nitrogen. Dichloromethane (CH\(_2\)Cl\(_2\)) and toluene were distilled from calcium hydride under dry nitrogen. MTBE is methyl tert-butyl ether. All reaction mixtures were stirred magnetically, unless otherwise noted.

**Keto Esters 10 and 7.** To a stirred suspension mixture of diethyl carbonate (205 mg, 1.74 mmol) and NaH (60%, 104 mg, 2.60 mmol) in DME (2 mL) was added a solution of tetracyclic ketone 8 (290 mg, 0.87 mmol) in DME (2.5 mL) followed by ETOH (5 μL) at rt under N\(_2\). The reaction mixture was heated to 90 °C and stirred at 90 °C for 4 h. The reaction mixture was thenpartitioned between cooled 5% aqueous HCl (10 mL) and MTBE. The combined organic extracts were washed with brine, dried (Na\(_2\)SO\(_4\)) and concentrated. The residue was chromatographed to produce the keto ester 10 (125 mg, 36% from 8) as a colorless oil: TLC \(R_f\) 0.78 (petroleum ether/MTBE = 7/3); IR (film) 2951, 2869, 1759, 1726, 1457, 1375, 1314, 1264, 1160, 1115, 1030, 925, 855 cm\(^{-1}\); 1H NMR δ 4.15–4.23 (m, 2H), 3.77 (t, J = 11.1 Hz, 1H), 3.53–3.62 (m, 2H), 3.04 (d, J = 13.0 Hz, 1H), 2.67–2.71 (m, 1H), 1.46–2.45 (m, 15H), 1.28 (t, J = 7.1 Hz, 3H), 1.01 (s, 3H), 0.86–0.91 (m, 9H), 0.67 (t, J = 12.8 Hz, 1H); 13C NMR δ up 210.3, 169.9, 101.3, 62.6, 61.7, 54.1, 37.9, 37.4, 35.6, 34.8, 27.7, 21.7; down 72.4, 52.5, 50.9, 47.7, 39.7, 29.0, 22.2, 18.3, 14.1; HRMS calcd for C\(_{24}\)H\(_{36}\)O\(_5\)Na (M + Na): 429.2617, found 429.2599. This was followed by the keto ester 7 (218 mg, 62% from 7) as a colorless oil, TLC \(R_f\) 0.28 (petroleum ether/MTBE = 7/3); IR (film) 2950, 2868, 1764, 1725, 1458, 1370, 1313, 1268, 1181, 1145, 1115, 1031, 925, 854 cm\(^{-1}\); 1H NMR δ 4.16–4.24 (m, 2H), 3.77 (t, J = 11.0 Hz, 1H), 3.67 (dd, J = 4.6, 11.0 Hz, 1H), 3.51–3.57 (m, 1H), 2.83 (s, 1H), 2.66–2.70 (m, 1H), 1.47–2.45 (m, 15H), 1.28 (t, J = 7.1 Hz, 3H), 1.03 (s, 3H), 0.86–0.91 (m, 9H), 0.70 (t, J = 12.8 Hz, 1H); 13C NMR δ up 208.9, 167.8, 101.5, 63.1, 60.9, 43.8, 37.4, 35.8, 34.9, 31.7, 27.7, 21.9; down 73.0, 51.1, 43.5, 38.8, 29.0, 24.5, 23.7, 22.2, 18.9, 14.9, 14.3; HRMS calcd for C\(_{23}\)H\(_{31}\)O\(_4\) (M + Na): 409.2617, found 429.2603.

**Keto Esters 10 and 7 from Ethyl Chloroformate and LDA.** To a stirred solution of the tetracyclic ketone 8 (290 mg, 0.87 mmol) in DME (2 mL) was added a solution of diisopropylamide (LDA) solution in THF (0.7 mL, 0.35 mmol) at –78 °C under N\(_2\). After an additional 1 h, ethyl chloroformate (45 mg, 0.34 mmol) in dry THF (0.7 mL) was added. The reaction mixture was thenpartitioned between cooled 5% aqueous HCl (10 mL) and MTBE. The combined organic extracts were washed with brine, dried (Na\(_2\)SO\(_4\)), and concentrated. The residue was chromatographed to give the keto ester 10 (13 mg, 51% from 8 based on 47% conversion). This was followed by the tetracyclic ketone 8 (24

mg) and then the keto ester 7 (3.5 mg, 14% from 8 based on 47% conversion).

**Tetrayclic Ketone 7 from Recycling the Keto Ester 10**

A stirred suspension mixture of keto ester 10 (25 mg, 0.062 mmol) and LiCl (13 mg, 0.31 mmol) in DMSO/H₂O (0.6 mL, DMSO/H₂O = 9/1, v/v) was heated to reflux for 30 min. After the mixture was cooled to rt, the reaction solvent was removed in vacuo. The residue was chromatographed to give the keto diol (9.5 mg, 78% from 10) as a colorless oil.

To a stirred solution of the keto diol (219 mg, 1.11 mmol), triethyl orthoformate (327 mg, 2.77 mmol), and (S)-(+-) mentholene (342 mg, 2.22 mmol) in dry THF (5 mL) was added a catalytic amount of p-TsOH·H₂O (21 mg, 0.11 mmol) at rt. After an additional 3 days, the reaction mixture was partitioned between CH₂Cl₂ and, sequentially, saturated aqueous NaHCO₃ and brine. The combined organic extracts were dried (Na₂SO₄) and concentrated. The residue was chromatographed to yield the tetrayclic ketone 8 (230 mg, 48% from 20).

**Diol Ketone 11 and Diol Ketal 12.** To a stirred solution of the keto ester 7 (336 mg, 0.83 mmol), triethyl orthoformate (491 mg, 3.32 mmol), and ethylene glycol (555 mg, 8.28 mmol) in dry CH₂Cl₂ (5.1 mL) was added benzenesulfonyl diol (9.5 mg, 78% from 6) and, sequentially, saturated aqueous NaHCO₃ and brine. The combined organic extracts were dried (Na₂SO₄) and concentrated. The crude residue was chromatographed to give the keto diol (9.5 mg, 78% from 10) as a colorless oil.

**Diol Benzenesulfonate 6.** To a stirred solution of monobenzenesulfonate 13 (44 mg, 0.32 mmol) in dry THF (10 mL) was added a 1 M solution of DIBAL-H in hexanes (1.6 mL, 1.60 mmol) at −78 °C under N₂. The reaction mixture was warmed slowly to rt over 1 h. After an additional 1 h at rt, the reaction mixture was partitioned between EtOAc and, sequentially, 5% aqueous HCl, saturated aqueous NaHCO₃, and brine. The organic extracts were dried (Na₂SO₄) and concentrated. The residue was chromatographed to yield the diol benzenesulfonate 13 (116 mg, 89% from 13) as a colorless oil: TLC Rₘ = 0.11 (EtOAc/petroleum ether = 4/1); IR (film) 3045, 2939, 1732, 1448, 1357, 1187, 1094, 914, 820, 732 cm⁻¹; ¹H NMR δ 7.85−7.97 (m, 2H), 7.66−7.72 (m, 1H), 7.56−7.60 (m, 2H), 4.34−4.48 (m, 1H), 3.44−3.98 (m, 8H), 1.25−2.71 (m, 11H), 0.78−0.87 (m, 3H); ¹³C NMR δ up 135.6, 116.8, 69.5, 64.8, 63.2, 58.8, 41.6, 38.9, 35.9, 30.6; down 133.9, 129.2, 127.8, 69.7, 59.9, 44.9, 42.5, 12.6; HRMS calc'd for C₂₀H₁₇O₃Na (M+Na) 435.1453, found 435.1443.

**Nitrile 16.** To a stirred solution of bromosulfone 15 (5.2 g, 15.6 mmol) in 1-methyl-2-pyrrolidinone (NMP) (120 mL) was added CuCN (7.0 g, 77.8 mmol). The reaction mixture was heated to reflux for 16 h and was then poured into 30% aqueous NH₄OH (300 mL) at 0 °C. After vigorous stirring for 3 h, the mixture was filtered, and the filter cake was partitioned between CH₂Cl₂ and brine. The combined organic extracts were dried (Na₂SO₄) and concentrated. The residue was recrystallized (EtOAc/petroleum ether = 1/1) to give the nitrile 16 (3.35 g, 75% from 25) as a white solid: TLC Rₘ = 0.21 (MTBE/petroleum ether = 1/1); mp 144−145 °C; IR (film) 2979, 2845, 2222, 1605, 1500 cm⁻¹; ¹H NMR δ 7.76 (d, J = 7.3 Hz, 2H), 7.70 (t, J = 8.8 Hz, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 1H), 7.13 (d, J = 2.5 Hz, 1H), 6.97 (d, J = 2.5 and 8.7 Hz, 1H), 4.56 (2H, s), 3.90 (3H, s); ¹³C NMR δ up 162.8, 137.6, 133.8, 117.0, 120.6, 60.7; down 134.50, 134.47, 129.5, 128.9, 117.5, 115.8, 56.0; HRMS calc'd for C₁₅H₁₃O₃NS: C, 62.70; H, 4.56; N, 8.47; Found: C, 62.60; H, 4.62; N, 4.98.

**Aldehyde 17.** To a stirred solution of nitrile 16 (3.92 g, 13.66 mmol) in THF (120 mL) was added a 0.83 M solution of DIBAL-H in hexanes (41.1 mL, 34.15 mmol) at −78 °C. The reaction mixture was warmed to rt over 2 h. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl and 6 M aqueous HCl (6:1, v/v) at 0 °C. The organic solvent was removed in vacuo, and the residue was then partitioned between EtOAc and brine. The combined organic extracts were dried (Na₂SO₄) and concentrated. The crude residue was recrystallized (EtOAc/petroleum ether = 20/1) to give the aldehyde 17 (3.22 g, 81% from 16) as a white solid: TLC Rₘ = 0.17 (MTBE/petroleum ether = 1/1); mp 114−115 °C; IR (film) 2939, 2841, 1638, 1599, 1571, 1447 cm⁻¹; ¹H NMR δ 9.68 (s, 1H), 7.70−7.72 (m, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.58−7.61 (m, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.00 (dd, J = 2.5 and 8.5 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 5.05 (s, 2H), 3.85 (3H, s); ¹³C NMR δ up 163.3, 138.2, 131.2, 127.9, 57.6; down 190.7, 137.2, 133.9, 128.9, 128.7, 119.4, 114.4, 55.8; HRMS calc'd for C₂₀H₁₉O₄S: C, 74.73; H, 7.24; Found: C, 73.24; H, 10.52.

**Sulfone 5.** The aldehyde 17 (2.50 g, 6.82 mmol), hydrazine monohydrate (50.7 g, 626.00 mmol), and K₂CO₃ (42.82 g, 310.32 mmol) were added into diethylene glycol (30 mL) sequentially. The mixture was heated at 180 °C for 5 h and then at 150 °C for another 16 h. The reaction mixture was cooled to rt and then partitioned between EtOAc and brine. The combined organic extracts were dried (Na₂SO₄) and concentrated. The crude residue was recrystallized (CH₂Cl₂/petroleum ether = 20/1) to give the sultone 5 (13.25 g, 37% from 17) as a white solid: TLC Rₘ = 0.33 (MTBE/petroleum ether J. Org. Chem., Vol. 67, No. 14, 2002}.
neutralized by the addition of saturated aqueous NaHCO₃, and the solvent was removed in vacuo. The residue was partitioned between EtOAc and H₂O. The combined organic extracts were dried (Na₂SO₄) and concentrated. The residue was chromatographed to yield the enone 4 (8 mg, 16% from 20) as a colorless oil: TLC Rᵣ = 0.37 (petroleum ether/methylene chloride/MeTHF = 7/2/1); [α]D ≈ −61.7 (c = 0.30, CH₂Cl₂); IR (film) 2956, 2926, 2865, 1712, 1639, 1610, 1499, 1458, 1377, 1299, 1252, 1208, 1160, 1103, 1046 cm⁻¹; ¹H NMR δ 7.04 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 2.7 Hz, 1H), 6.66 (dd, J = 2.7, 8.2 Hz, 1H), 3.76 (t, J = 7.5 Hz, 1H), 3.78 (3H, s), 2.45–2.73 (m, 6H), 2.34 (dd, J = 7.2, 17.3 Hz, 1H), 2.27 (m, 3H, J = 6.6 Hz, 2H), 1.34–2.00 (m, 9H), 1.21 (s, 3H), 1.16–1.25 (m, 1H), 0.86 (d, J = 6.6 Hz, 6H); ¹³C NMR δ up 210.4, 205.8, 157.8, 145.7, 141.6, 128.0, 43.1, 39.9, 38.51, 38.47, 35.5, 31.1, 27.83, 27.78, 27.71; down 138.1, 131.0, 114.5, 111.1, 55.2, 49.2, 46.9, 27.80, 22.57, 22.53, 19.4, 18.4; HRMS calcd for C₁₃H₁₅O₂Na (M + Na) 433.2719, found 433.2704. This was followed by the enone 21 (8.5 mg, 17% from 20) as a colorless oil: TLC Rᵣ = 0.35 (petroleum ether/methylene chloride/MeTHF = 7/2/1); [α]D ≈ −41.7 (c = 0.30, CH₂Cl₂); IR (film) 2954, 2921, 2865, 1710, 1644, 1608, 1503, 1455, 1377, 1299, 1252, 1204, 1160, 1102, 1046 cm⁻¹; ¹H NMR δ 7.04 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 2.7 Hz, 1H), 6.66 (dd, J = 2.7, 8.2 Hz, 1H), 6.53 (t, J = 7.8 Hz, 1H), 3.78 (3H, s), 2.45–2.74 (m, 6H), 2.38 (dd, J = 6.9, 17.0 Hz, 1H), 2.27 (s, 3H), 2.17–2.29 (m, 3H), 1.99–2.10 (m, 3H), 1.81–1.86 (m, 1H), 1.65–1.72 (m, 1H), 1.45–1.57 (m, 3H), 1.27 (3H, s), 1.21–1.25 (m, 1H), 0.87 (d, J = 6.6 Hz, 6H); ¹³C NMR δ up 210.2, 204.8, 157.4, 145.0, 141.5, 128.0, 43.0, 38.74, 38.68, 38.35, 37.10, 31.0, 28.11, 27.57, 22.17, 15.47, 11.11, 55.2, 49.1, 47.3, 22.51, 22.49, 18.4, 17.8; HRMS calcd for C₁₃H₁₅O₂Na (M + Na) 433.2719, found 433.2715.

**Enone 4 from Enone 21.** To a stirred solution of enone 22 (6 mg, 0.015 mmol) in HOAc (0.5 mL) was added KI (25 mg, 0.15 mmol) at rt. After an additional 2 days, the reaction solvent was removed in vacuo. The residue was partitioned between MTBE and, sequentially, saturated aqueous NaHCO₃ and brine. The combined organic extracts were dried (Na₂SO₄) and concentrated. The residue was chromatographed to give the enone 4 (2.2 mg, 69% from 21) based on 53% conversion) as a colorless oil. This was followed by the enone 21 (2.8 mg) as a colorless oil.

**Dione 22.** To a stirred suspension mixture of Cu (38 mg, 0.20 mmol) in dry EtO (1.2 mL) was added a 2.2 M solution of MeLi in Et₂O (0.18 mL, 0.40 mmol) dropwise at −20 °C under N₂. After an additional 1 h, the reaction mixture was added a solution of the enone 4 (8 mg, 0.020 mmol) in dry EtO (0.8 mL), and the reaction mixture was then stirred for another 1 h at −20 °C. The reaction mixture was partitioned between CH₂Cl₂ and, sequentially, saturated aqueous NH₄Cl and brine. The combined organic extracts were dried (Na₂SO₄) and concentrated. The residue was chromatographed to provide the dione 22 (5.5 mg, 66% from 4) as a colorless oil: TLC Rᵣ = 0.40 (petroleum ether/methylene chloride/MTBE = 7/2/1); [α]D ≈ −85.7 (c = 0.28, CH₂Cl₂); IR (film) 2954, 2921, 2865, 1738, 1709, 1608, 1500, 1464, 1383, 1299, 1252, 1209, 1160, 1104, 1046 cm⁻¹; ¹H NMR δ 7.04 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 2.7 Hz, 1H), 6.66 (dd, J = 2.7, 8.2 Hz, 1H), 3.78 (3H, s), 2.71 (dd, J = 4.8, 11.6, 13.2 Hz, 1H), 2.28–2.56 (m, 6H), 2.27 (3H, s), 1.14–2.03 (m, 14H), 1.09 (3H, s), 1.01 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H); ¹³C NMR δ up 216.2, 210.4, 157.8, 141.6, 128.0, 43.2, 39.7, 39.1, 38.4, 35.8, 31.8, 28.01, 24.9; down 131.0, 114.6, 111.0, 67.7, 55.2, 49.1, 48.5, 31.16, 27.94, 22.7, 22.6, 18.7, 18.4, 13.2.

**Diol 23.** To a stirred solution of dione 22 (5.5 mg, 0.013 mmol) in dry THF (1 mL) was added a 1 M solution of L-Selectride in THF (0.13 mL, 0.13 mmol) at −78 °C. The reaction mixture was slowly warmed to rt over 1.5 h. After an additional 0.5 h at rt, the reaction mixture was partitioned between EtOAc and, sequentially, saturated aqueous NaHCl and brine. The combined organic extracts were dried (Na₂SO₄) and concentrated. The residue was chromatographed to give
the diol 23 (2.5 mg, 45% from 22) as a colorless oil: TLC Rf = 0.28 (petroleum ether/methylene chloride/MTBE = 7:2:1); [α]D 20 = -5.6 (c = 0.13, CHCl3); IR (film) 3418, 2928, 2865, 1614, 1505, 1456, 1363, 1306, 1251, 1208, 1160, 1102, 1046 cm⁻¹; 1H NMR δ 7.04 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 6.65 (dd, J = 2.7, 8.2 Hz, 1H), 4.32–4.37 (m, 1H), 4.06 (d, J = 1.3 Hz, 1H), 3.78 (s, 3H), 2.73 (dd, J = 4.5, 11.2, 13.2 Hz, 1H), 2.43–2.50 (m, 1H), 2.24 (s, 3H), 2.18–2.27 (m, 1H), 1.06–1.78 (m, 20H), 0.99 (d, J = 6.6 Hz, 3H), 0.90 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); 13C NMR δ up 157.8, 142.3, 127.8, 39.5, 36.5, 36.2, 34.2, 31.1, 30.3, 29.9, 24.1, down 130.9, 114.5, 110.8, 71.9, 67.0, 61.3, 55.2, 45.4, 40.4, 29.7, 28.1, 22.8, 22.6, 18.3, 18.2, 12.1; HRMS calcd for C₁₉H₂₅O₄N₄aNa (M + Na) 453.3345, found 453.3337.

**Calicoferol B (1).** To a stirred solution of diol 23 (2.3 mg, 0.0054 mmol) and Et₃SiH (25 mg, 0.22 mmol) in dry CH₂Cl₂ (1 mL) was added a solution of (C₆F₅)₃B (0.6 mg, 0.0012 mmol) and Et₃N (0.1 mL) was added, and the reaction mixture was filtered through a short pad of silica gel. The filter cake was washed with MTBE, and the filtrate was concentrated. The residue was used in the next step without further purification.

The residue dissolved in a 1 M solution of TBAF in THF (0.8 mL) at rt. After an additional 24 h, the reaction mixture was partitioned between ETOAc and, sequentially, saturated aqueous NH₄Cl and brine. The combined organic extracts were washed with MTBE, and the filtrate was concentrated. The residue was used in the next step without further purification.

The reaction was performed with the dione 24 (2.7 mg, 0.0063 mmol), L-Selectride (1 M in THF, 0.13 mL, 0.13 mmol), and dry THF (0.5 mL) in the same manner as described for the preparation of diol 23 to give diol 25 (1.2 mg, 16% from 21) as a colorless oil: TLC Rf = 0.20 (petroleum ether/methylene chloride/MTBE = 7:2:1); 1H NMR δ 7.04 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 2.7 Hz, 1H), 6.65 (dd, J = 2.7, 8.2 Hz, 1H), 4.30–4.35 (m, 1H), 4.06 (brs, 1H), 3.78 (s, 3H), 2.70–2.77 (m, 1H), 2.42–2.50 (m, 1H), 2.24 (s, 3H), 2.13–2.28 (m, 1H), 1.05–1.90 (m, 20H), 0.98 (d, J = 6.4 Hz, 3H), 0.91 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H).

**C(20)-epi-Calicoferol B (26).** The reaction was performed with the diol 25 (1.2 mg, 0.0028 mmol), Et₂SiH (13 mg, 0.11 mmol), (C₆F₅)₃B (0.3 mg, 0.00059 mmol), and dry CH₂Cl₂ (0.6 mL); Et₃N (0.1 mL); TBAF (1 M in THF, 0.5 mL); in the same manner as described for the preparation of calicoferol B (1) to give C(20)-epi-calicoferol B (26) (0.8 mg, 69% from 25) as a colorless oil: TLC Rf = 0.40 (petroleum ether/MTBE = 1:1); [α]D 20 +52.8 (c = 0.053, CHCl₃); IR (film) 3380, 2925, 2858, 1653, 1610, 1497, 1464, 1384, 1257, 1158, 1102, 1024 cm⁻¹; 1H NMR (CD₃OD) δ 6.94 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 2.7 Hz, 1H), 6.44 (dd, J = 2.7, 8.2 Hz, 1H), 3.96 (dd, J = 4.3, 7.6, 7.6 Hz, 1H), 3.71 (d, J = 2.4 Hz, 1H), 2.68 (dd, J = 5.0, 12.8, 13.2 Hz, 1H), 2.34 (dd, J = 5.0, 11.7, 13.3 Hz, 1H), 2.23 (s, 3H), 1.93–2.11 (m, 2H), 1.15–1.70 (m, 19H), 1.07 (dd, J = 4.2, 12.9 Hz, 1H), 0.97 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 7.1 Hz, 6H), 0.92 (s, 3H); 13C NMR (CD₃OD) δ up 155.2, 143.3, 43.4, 40.2, 37.6, 35.5, 35.1, 31.6, 31.3, 30.8, 24.8; down 131.7, 116.4, 113.2, 72.3, 67.0, 62.0, 46.0, 41.2, 30.2, 28.9, 23.4, 23.2, 19.3, 18.9, 12.8; HRMS calcd for C₂₇H₄₄O₃Na (M + Na) 439.3188, found 439.3176.

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**Supporting Information Available:** 1H and 13C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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