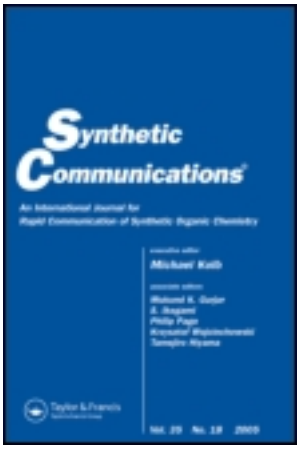

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Total Synthesis of (±)-Calanolide A

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TOTAL SYNTHESIS OF (±)-CALANOLIDE A

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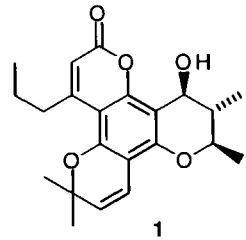
Abstract: The total synthesis of (±)-Calanolide A, incorporating a ring-forming sequence different from previous procedures, is described.

Calanolide A (**1**), a dipyranocoumarin isolated from the leaves and twigs of the tropical rainforest tree *Calophyllum lanigerum* var. *austrocoriaceum*, has been recently identified as a potent representative of a pharmacologically distinct subclass of non-nucleosidal human immunodeficiency virus-1 (HIV-1) specific reverse transcriptase inhibitors.[1] In addition, **1** was reported to have shown activity against the azidothymidine-resistant HIV-1 strain G-9106 and the pyridinone-resistant HIV-1 strain A17.[1] Since the extraction and isolation from the crude leaves and twigs provides only about 0.1%[2] of **1**, there is an inadequate supply available for detailed preclinical trials. This deficiency could be circumvented by the total synthesis of **1** from readily available starting materials. In this paper we describe the total synthesis of (±)-**1**.[3a-f]

* To whom correspondence should be addressed

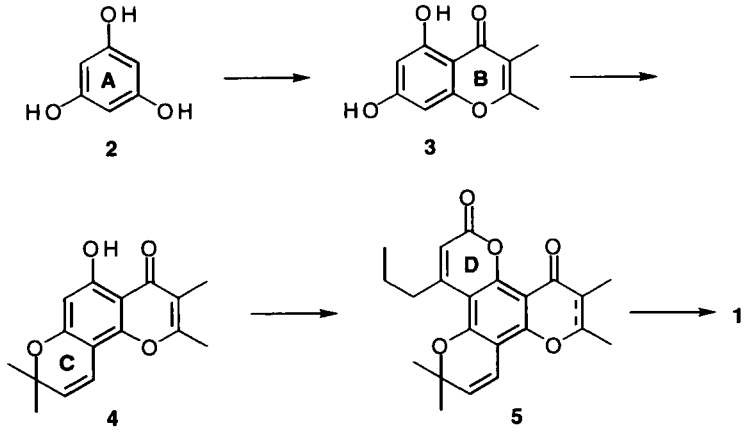


1

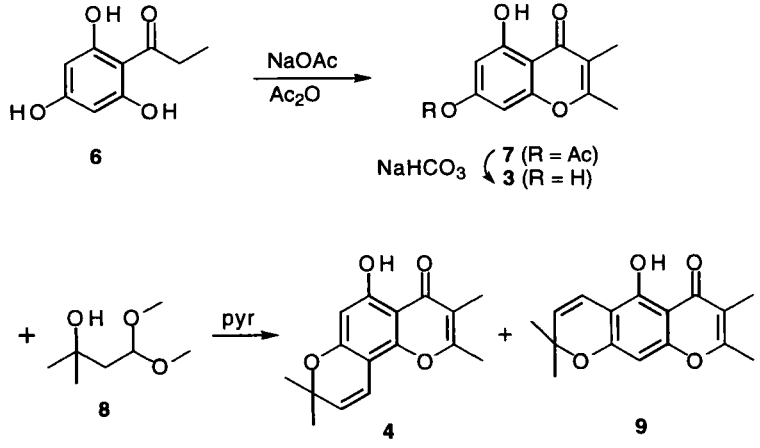
One possible strategy for the synthesis of **1** is a series of ring forming reactions (Scheme 1), starting with a phloroglucinol (**2**) core (ring A). The order of ring-formation would depend primarily on the regiochemical preference of the second ring-forming step. The synthesis of **3** from a substituted phloroglucinol has been described[4]; the regiochemical preference for formation of the angular derivative (rather than the linear) in the ring C forming step (**3** to **4**) has been previously established[5]; and the formation of ring D from a substrate similar to **4** is known.[6] The timing of ring B reduction in this sequence, however, was unclear. With this strategy in hand, the total synthesis of (±)-**1** was begun. The Kostanecki-Robinson reaction[4] of 2,4,6-trihydroxypropiophenone (**6**) using sodium acetate in refluxing acetic anhydride, followed by deacetylation[7] of resultant **7** afforded **3** in 45% yield from **6** (Scheme 2). Reaction of **3** with 1,1-dimethoxy-3-hydroxy-3-methylbutane **8**[5] in pyridine gave a 3:1 mixture of **4** and **9**, from which a 41% yield of pure **4** and a 15% yield of pure **9** was isolated by chromatography.

Structural assignment of **4** and **9** was made on the basis of their NOE difference spectra. Especially diagnostic was the enhancement between the phenolic proton and the aromatic proton in **4**, and the phenolic proton and the vinyl proton in **9**. Additional confirmation was provided by the

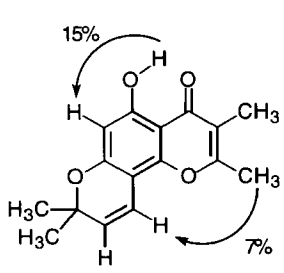
Scheme 1



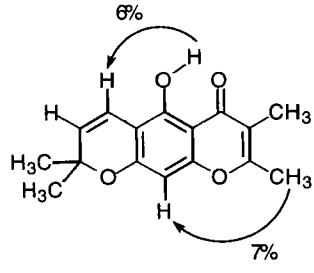
Scheme 2



enhancement between the 2-methyl and the vinyl proton in **4**, and the 2-methyl and the aromatic proton in **9**.



4

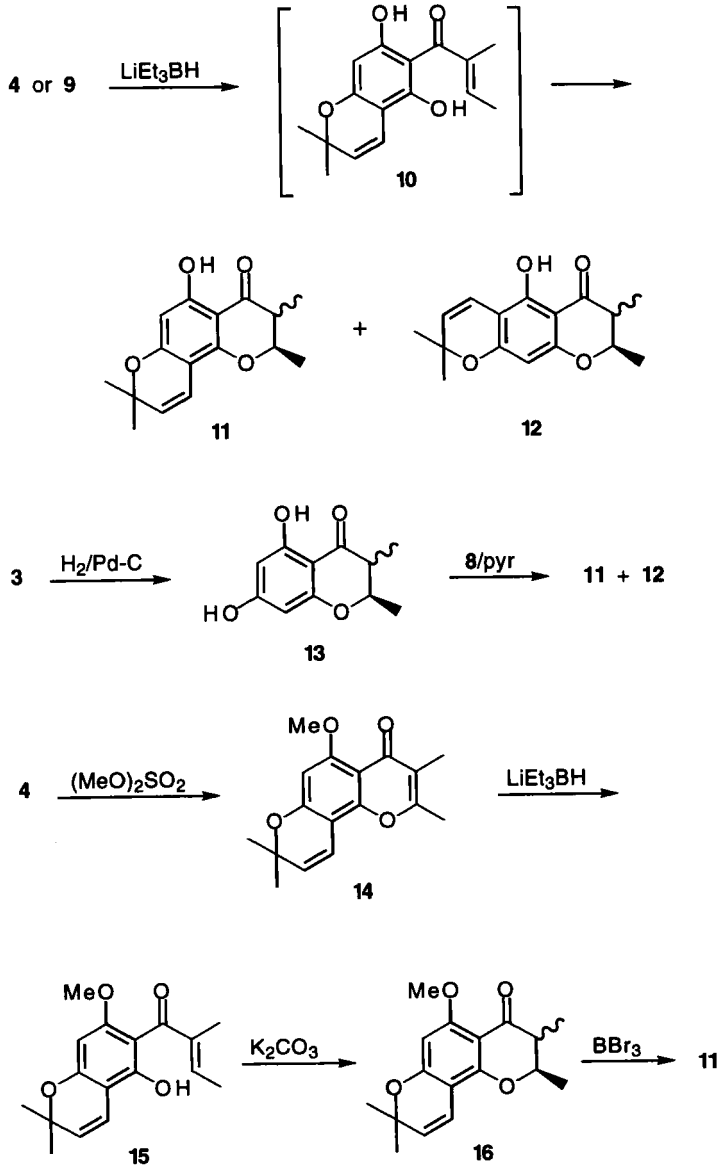


9

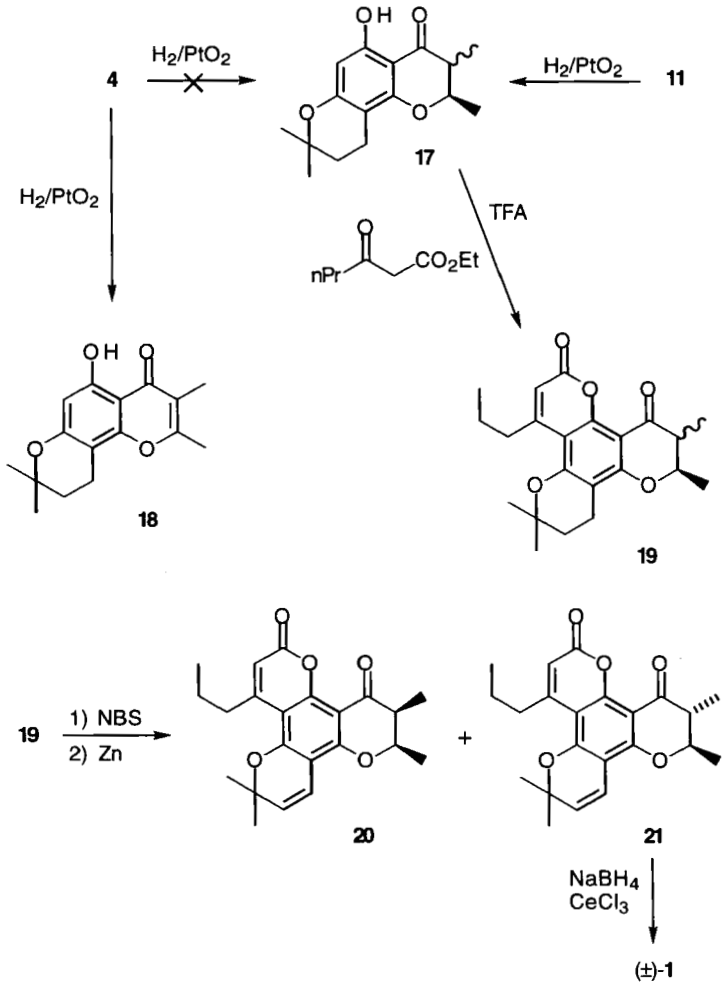
Reduction of **4** (or **9**) with lithium triethylborohydride gave a mixture of four compounds, tentatively assigned as cis- and trans-**11** and cis- and trans-**12** (Scheme 3), suggesting the existence of common ring-opened intermediate **10**. One strategy to avoid the undesirable rearrangement of **4** to **12** would be to reduce ring B prior to ring C construction. Accordingly, **3** was hydrogenated with 10% palladium on carbon to give **13**; unfortunately, cyclization of **13** with **8** gave a 1:2 mixture (^{1}H NMR) of cis/trans-**11** and cis/trans-**12**. Rearrangement of **4** to **12** was avoided by protecting **4** as its' methyl ether **14**, prepared in 98% yield by reaction of **4** with dimethylsulfate; reduction of **14** with lithium triethylborohydride followed by treatment of resultant **15** with potassium carbonate afforded **16**.[8] Demethylation of **16** with boron tribromide[9] gave desired **11**.

Attempted formation of ring D by reaction of **11** with ethyl butyrylacetate under various von Pechmann[10] reaction conditions, including concentrated sulfuric acid, neat trifluoroacetic acid, and neat trifluoromethanesulfonic acid, led to decomposition but no desired **21** (Scheme 4).

Scheme 3



Scheme 4



This result contrasts with earlier work by Stout[6], who was able to effect a similar transformation on **17**, a dihydro congener of **11**. Attempts to synthesize **17** by hydrogenation of **4** gave only **18**. Synthesis of **17** was accomplished by hydrogenation of **11**; subsequent treatment with ethyl butyrylacetate in refluxing trifluoroacetic acid gave **19**.[6] Bromination of **19**

with N-bromosuccinimide followed by *in situ* dehydrohalogenation afforded **21**, along with what appeared to be a small amount of α-bromo ketone side product which could not be separated. Treatment of this mixture with zinc afforded a mixture of **21** and **20** which was separated by chromatography. Reduction of **21** with sodium borohydride in the presence of cerium chloride[11] gave (±)-**1**, whose ^{1}H NMR, ^{13}C NMR and mass spectrum were in complete agreement with those published for natural Calanolide A.[2] This total synthesis of (±)-Calanolide A should prove an alternative starting point for structure-activity studies of this class of compounds.

Experimental Section

General Procedures. All reagent grade chemicals and solvents were purchased from commercial suppliers and were used without further purification, unless otherwise noted. All reactions were performed at room temperature under nitrogen using oven dried glassware, unless otherwise noted. For all reactions using an extraction as part of the workup, the combined organic extracts were dried over Na_2SO_4 and the solvents removed *in vacuo* prior to chromatography, unless otherwise noted. Flash column chromatography was performed with Merck Kieselgel 60 (230 - 400 mesh ASTM) silica. Analytical thin-layer chromatography was performed on precoated silica gel plates (0.25 mm 60 F-254 E. Merck) and were visualized with UV light or iodine. Melting points were obtained on a capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured at 250 and 63 MHz, respectively, in $CDCl_3$ unless otherwise noted; ^{1}H chemical shifts are reported in δ (ppm) downfield from TMS (0.0 ppm) as an internal standard; ^{13}C NMR shifts are reported in δ

(ppm) measured relative to the center resonance of $^{13}CDCl_3$ (77.0 ppm) or $^{13}CD_3OD$ (49.0 ppm); *J* values are in Hertz. Infrared spectra were obtained as $CHCl_3$ solutions. Mass spectra were obtained at an ionizing voltage of 70 eV, unless otherwise noted. Elemental analyses were obtained from Atlantic Microlab.

7-Acetoxy-2,3-dimethyl-5-hydroxy-4*H*-1-benzopyran-4-one (7). A solution of **6** (12.7 g, 69.7 mmol), Ac_2O (40 mL, 423.9 mmol), and NaOAc (5.0 g, 61.0 mmol) was refluxed 14 h, cooled and diluted with H_2O, then extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O until the aqueous washes were neutral to pH paper, dried and the solvent removed. Flash chromatography (3:1 hexane-EtOAc) gave **7** (9.7 g, 56% yield): *Rf* 0.23 (5:1 hexane-EtOAc); mp 134-138 °C; ^1H NMR δ 2.01 (s, 3), 2.31 (s, 3), 2.39 (s, 3), 6.49 (d, 1, *J* = 1.5), 6.64 (d, 1, *J* = 1.5), 12.95 (s, 1); ^{13}C NMR δ 9.11, 18.48, 21.12, 100.30, 104.55, 107.73, 115.69, 155. 31, 156.40, 161.66, 163.45, 168.37, 182.18; MS (EI) *m/z* (rel. int.) 248 (31), 206 (100), 191(23), 177 (12), 163 (10), 153 (13), 123 (15), 43 (76); IR cm^{-1} 3010, 1769, 1654, 1625, 1602, 1488, 1370, 1292, 1193, 1017. Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.85; H, 4.90.

5,7-Dihydroxy-2,3-dimethyl-4*H*-1-benzopyran-4-one (3). A solution of **7** (2.02 g, 8.14 mmol) in a 1:1 mixture of MeOH and saturated aqueous $NaHCO_3$ (150 mL) was stirred 20 h, then acidified with 3 N HCl and extracted with CH_2Cl_2. Flash chromatography (2:1 hexane-EtOAc) gave **3** (1.39 g, 83% yield): *Rf* 0.11 (5:1 hexane-EtOAc); mp 211-214 °C (Lit.[12] mp 216-217.5 °C); ^1H NMR (CD_3OD) δ 1.91 (s, 3), 2.32 (s, 3), 6.11 (d, 1, *J* = 2.1), 6.17 (d, 1, *J* = 2.1); ^{13}C NMR (CD_3OD) δ 9.15, 18.36, 94.25, 99.49, 104.53, 115.58, 159.11, 163.01, 164.44, 165.33, 183.02; MS

(EI) *m/z* (rel. int.) 206 (100), 191 (41), 177 (16), 163 (25), 153 (32), 124 (17), 69 (42); IR cm^{-1} 3455, 2995, 1657, 1633, 1338, 1144. Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.01; H, 4.91.

5-Hydroxy-2,3,8,8-tetramethyl-4*H*,8*H*-benzo[1,2-b:3,4-b']dipyran-4-one (4) and 5-Hydroxy-2,3,8,8-tetramethyl-4*H*,8*H*-benzo[1,2-b:4,5-b']dipyran-4-one (9). A solution of **3** (1.01 g, 4.92 mmol) and **8**[6] (0.80 g, 5.40 mmol) in anhydrous pyridine (0.40 mL, 4.95 mmol) was heated in a sealed tube at 140 °C for 20 h, then cooled and the solvent removed *in vacuo*. Flash chromatography (10:1 hexane-EtOAc) gave **4** (0.55 g, 41% yield) and **9** (0.20 g, 15% yield): **4**: R_f 0.39 (5:1 hexane-EtOAc); mp 187 °C; ^{1}H NMR δ 1.45 (s, 6), 1.98 (s, 3), 2.37 (s, 3H), 5.54 (d, 1, J = 10.0), 6.21 (s, 1), 6.63 (d, 1, J = 10.0), 13.03 (s, 1); ^{13}C NMR δ 9.08, 18.31, 28.08, 77.75, 99.58, 100.56, 104.33, 114.78, 115.01, 126.89, 151.75, 158.89, 161.55, 162.06, 181.92; MS (EI) *m/z* (rel. int.) 272 (23), 257 (100), 203 (19); IR cm^{-1} 3005, 1657, 1573, 1473, 1429, 1333, 1179, 1151, 1106. Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.59; H, 5.91. **9**: R_f 0.44 (5:1 hexane-EtOAc); mp 102 °C; ^{1}H NMR δ 1.45 (s, 6), 1.97 (s, 3), 2.33 (s, 3), 5.58 (d, 1, J = 10.0), 6.20 (s, 1), 6.69 (d, 1, J = 10.0), 13.26 (s, 1); ^{13}C NMR δ 9.05, 18.33, 28.17, 77.64, 94.25, 104.38, 104.93, 114.80, 115.53, 127.70, 156.21, 156.80, 158.85, 162.31, 181.86; MS (EI) *m/z* (rel. int.) 272 (18), 257 (100), 203 (6); IR cm^{-1} 3000, 1654, 1621, 1593, 1467, 1374, 1336, 1295, 1192, 1149, 1104, 1077. Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.62; H, 5.93.

5-Methoxy-2,3,8,8-tetramethyl-4*H*,8*H*-benzo[1,2-b:3,4-b']dipyran-4-one (14). A solution of **4** (0.630 g, 2.31 mmol), $(MeO)_2SO_2$ (0.60 mL, 6.33 mmol), and K_2CO_3 (0.540 g, 3.90 mmol) in acetone (40.0 mL) was refluxed 48 h, cooled and diluted with Et_2O, then washed with saturated

aqueous NH_4Cl. Flash chromatography (1:1 hexane-EtOAc) gave **14** (0.650 g, 98%): *Rf* 0.04 (5:2 hexane-EtOAc); mp 232-233 °C; ^1H NMR δ 1.46 (s, 6), 1.96 (s, 3), 2.32 (s, 3), 3.92 (s, 3), 5.54 (d, 1, *J* = 10.0), 6.26 (s, 1), 6.68 (d, 1, *J* = 10.0); ^{13}C NMR δ 9.89, 17.82, 28.05, 56.14, 77.70, 95.86, 101.87, 107.74, 115.24, 117.40, 126.84, 153.56, 157.02, 158.16, 160.48, 177.01; MS (EI) *m/z* (rel. int.) 286 (29), 271 (100), 257 (18), 242 (9), 227 (4), 217 (22), 202 (6); IR cm^{-1} 3000, 1655, 1620, 1574, 1407, 1337, 1197, 1147, 1114, 1015. Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.09; H, 6.41.

2,2-Dimethyl-5-hydroxy-7-methoxy-6-(2-methyl-2-buten-1-onyl)-2*H*-1-benzopyran (15). $LiEt_3BH$ (1.0 M in THF; 2.20 mL, 2.20 mmol) was added to a solution of **14** (0.617 g, 2.15 mmol) in anhydrous THF (20.0 mL), stirred 15 min, then quenched with saturated aqueous NH_4Cl and extracted with Et_2O. Flash chromatography (3:1 hexane-EtOAc) gave **15** (0.446 g, 72% yield): *Rf* 0.35 (5:1 hexane-EtOAc); mp 112 °C; ^1H NMR δ 1.45 (s, 6), 1.76 (dd, 3, *J* = 1.0, 7.0), 1.85 (d, 3, *J* = 1.2), 3.72 (s, 3), 5.45 (d, 1, *J* = 10.0), 5.88 (s, 1), 5.98 (dq, 1, *J* = 1.2, 7.0), 6.64 (d, 1, *J* = 10.0), 12.27 (s, 1); ^{13}C NMR δ 13.21, 13.88, 28.33, 55.54, 77.91, 91.62, 102.85, 105.13, 116.03, 125.44, 130.11, 140.07, 159.61, 159.76, 161.65, 201.66; MS (EI, 14 eV) *m/z* (rel. int.) 288 (30), 273 (80), 217 (100); IR cm^{-1} 3005, 1640, 1609, 1576, 1289, 1141, 1121. Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99; Found: C, 71.09; H, 7.24.

***trans* and *cis*-2,3-Dihydro-5-methoxy-2,3,8,8-tetramethyl-4*H*,8*H*-benzo[1,2-b:3,4-b']dipyran-4-one (16).** A solution of **15** (0.810 g, 2.81 mmol) and K_2CO_3 (0.800 g, 5.79 mmol) in acetone (40.0 mL) was refluxed for 24 h, then quenched with saturated NH_4Cl and extracted with Et_2O. Flash chromatography (5:1 hexane-EtOAc) gave *trans*-**16** (0.305 g,

38% yield) and *cis*-**16** (0.250 g, 31% yield): *trans*-**16**: R_f 0.16 (5:1 hexanes-EtOAc); mp 146 °C; ^{1}H NMR δ 1.16 (d, 3, J = 7.0), 1.42 (s, 3), 1.44 (s, 3), 1.47 (d, 3, J = 6.3), 2.45 (dq, 1, J = 7.0, 11.0), 3.86 (s, 3), 4.16 (dq, 1, J = 6.3, 11.0), 5.47 (d, 1, J = 10.0), 6.01 (s, 1), 6.58 (d, 1, J = 10.0); ^{13}C NMR δ 10.68, 19.63, 28.07, 28.38, 47.16, 56.00, 77.74, 78.68, 93.32, 102.40, 104.89, 115.89, 126.00, 158.32, 159.45, 161.99, 192.11; MS (EI) m/z (rel. int.) 288 (28), 273 (72), 217 (100), 202 (1); IR cm^{-1} 3005, 1711, 1668, 1631, 1599, 1573, 1478, 1339, 1234, 1152, 1121. Anal. Calcd. for $C_{17}H_{20}O_4 \cdot 1/4\ (H_2O)$: C, 69.72; H, 7.06. Found: C, 69.51; H, 6.94. *cis*-**16**: R_f 0.09 (5:1 hexane-EtOAc); ^{1}H NMR δ 1.13 (d, 3, J = 7.3), 1.38 (d, 3, J = 6.6), 1.45 (s, 6), 2.52 (dq, 1, J = 3.2, 7.3), 3.87 (s, 3), 4.57 (dq, 1, J = 3.2, 6.6), 5.47 (d, 1, J = 10.0), 6.01 (s, 1), 6.58 (d, 1, J = 10.0); ^{13}C NMR δ 9.38, 16.30, 28.23, 28.41, 46.10, 56.09, 76.15, 77.83, 93.37, 102.44, 104.12, 115.98, 126.00, 155.95, 158.33, 159.61, 162.37, 194.14; MS (EI) *m/z* (rel. int.) 288 (21), 273 (63), 217 (100), 202 (10); IR cm^{-1} 3000, 1715, 1667, 1638, 1603, 1565, 1477, 1347, 1278, 1155, 1125. Anal. Calcd. for $C_{17}H_{20}O_4 \cdot 1/4\ (H_2O)$: C, 69.72; H, 7.06. Found: C, 69.82; H, 7.03.

***trans* and *cis*-2,3-Dihydro-5-hydroxy-2,3,8,8-tetramethyl-4*H*,8*H*-benzo[1,2-b:3,4-b']dipyran-4-one (11).** BBr_3 (1.0 M in CH_2Cl_2; 2.00 mL, 2.00 mmol) was added to a -78 °C solution of a 1:1 mixture of *trans*-**16** and *cis*-**16** (0.554 g, 1.92 mmol) in anhydrous CH_2Cl_2 (20.0 mL). The reaction was stirred 30 min, warmed to 25 °C and stirred 30 min, then quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. Flash chromatography (20:1 hexane-EtOAc) gave *trans*-**11** (0.256 g, 49% yield) and *cis*-**11** (0.184 g, 34% yield): *trans*-**11**: R_f 0.46 (5:1 hexane-EtOAc); mp 89-91 °C; ^{1}H NMR δ 1.21 (d, 3, J = 7.0), 1.52 (d, 3, J = 6.3),

1.58 (s, 6), 2.56 (dq, 1, J = 7.0, 11.2), 4.20 (dq, 1, J = 6.3, 11.2), 5.47 (d, 1, J = 10.0), 5.96 (s, 1), 6.53 (d, 1, J = 10.0), 12.23 (s, 1); ^{13}C NMR δ 10.13, 19.60, 28.18, 28.45, 45.56, 77.92, 78.99, 97.25, 101.48, 102.04, 115.52, 126.19, 156.58, 161.84, 163.71, 198.51; MS (EI) *m/z* (rel. int.) 274 (29), 259 (100), 217 (2), 203 (71); IR cm^{-1} 3010, 1644, 1582, 1386, 1350, 1275, 1158, 1124, 1092. Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.01; H, 6.85. *cis*-**11**: *Rf* 0.40 (5:1 hexane-EtOAc); ^{1}H NMR δ1.18 (d, 3, J = 7.3), 1.39 (d, 3, J = 6.6), 1.43 (s, 6), 2.54 (dq, 1, J = 3.2, 7.3), 4.58 (dq, 1, J = 3.2, 6.6), 5.48 (d, 1, J = 10.0), 5.95 (s, 1), 6.54 (d, 1, J = 10.0), 12.17 (s, 1); ^{13}C NMR δ 9.36, 16.35, 28.18, 28.35, 44.15, 76.19, 77.87, 97.16, 101.28, 101.42, 115.48, 126.06, 156.43, 161.84, 164.00, 200.47; MS (EI) *m/z* (rel. int.) 274 (14), 259 (79), 203 (100); IR cm^{-1} 2970, 1639, 1588, 1473, 1364, 1312, 1268, 1161, 1101. Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.92; H, 6.74.

***trans* and *cis*-2,3,6,7-Tetrahydro-5-hydroxy-2,3,8,8-tetramethyl-4*H*,8*H*-benzo[1,2-b:3,4-b']dipyran-4-one (17).** PtO_2 (approximately 5 mg) was added to a solution of a 1:1 mixture of *trans*-**11** and *cis*-**11** (0.098 g, 0.36 mmol) in MeOH (20.0 mL) under a H_2 atm. The reaction was stirred 30 min, then quenched with saturated aqueous NH_4Cl and extracted with Et_2O. Flash chromatography (20:1 hexane-EtOAc) gave *trans*-**17** (0.042 g, 43% yield) and *cis*-**17** (0.044 g, 45% yield): *trans*-**17**: *Rf* 0.10 (20:1 hexane-EtOAc); mp 120 °C; ^{1}H NMR δ 1.21 (d, 3, J = 7.0), 1.25 (s, 3), 1.32 (s, 3), 1.51 (d, 3, J = 6.3), 1.76 (m, 2), 2.55 (m, 3H), 4.18 (dq, 1, J = 7.0, 11.2), 5.92 (s, 1), 11.90 (s, 1); ^{13}C NMR δ 10.17, 16.06, 19.67, 26.33, 27.11, 31.92, 45.45, 75.92, 78.84, 97.07, 100.21, 101.75, 159.53, 161.34, 162.55, 198.43; MS (EI) *m/z* (rel. int.) 276 (65), 261 (30), 221 (100), 205 (37); IR cm^{-1} 2965, 1644, 1618, 1581, 1478, 1444, 1352,

1155, 1116, 1095. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55%; H, 7.30%. Found: C, 69.60; H, 7.32. *cis*-**17**: R_f 0.06 (20:1 hexane-EtOAc); mp 103 - 105 °C; ^{1}H NMR δ 1.17 (d, 3, J = 7.3), 1.33 (s, 3), 1.40 (d, 3, J = 6.6), 1.76 (m, 2), 2.53 (m, 3), 4.57 (dq, 1, J = 3.2, 6.6), 5.92 (s, 1), 11.83 (s, 1); ^{13}C NMR δ 9.37, 16.04, 16.44, 26.47, 26.89, 31.84, 44.14, 75.92, 76.07, 97.05, 100.27, 101.04, 159.47, 161.64, 162.64, 200.52; MS (EI) *m/z* (rel. int.) 276 (68), 261 (30), 221(100), 205 (36); IR cm^{-1} 2945, 1637, 1616, 1582, 1469, 1375, 1340, 1307, 1152, 1107. Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.53; H, 7.33.

***trans* and *cis*-4-Propyl-7,8,10,11-tetrahydro-6,6,10,11-tetramethyl-2*H*,6*H*,12*H*-benzo[1,2-b:3,4-b':5,6-b'']tripyran-2,12-dione (19).** A solution of a 1:1 mixture of *trans*-**17** and *cis*-**17** (0.153 g, 0.55 mmol) and ethyl butyrylacetate (0.20 mL, 1.24 mmol) in TFA (2.5 mL) was refluxed 20 h, then cooled, quenched with H_2O, and extracted with Et_2O. Flash chromatography (5:2 hexane-EtOAc) gave *trans*-**19** (0.102 g, 50% yield) and *cis*-**19** (0.086 g, 42% yield): *trans*-**19**: R_f 0.10 (5:2 hexane-EtOAc); mp 162 °C (Lit.[6] mp 163-165 °C); ^{1}H NMR δ 0.98 (t, 3, J = 7.3), 1.18 (d, 3, J = 6.9), 1.39 (s, 3), 1.41 (s, 3), 1.51 (d, 3, J = 6.3), 1.58 (m, 2), 1.82 (m, 2), 2.50 (m, 1), 2.66 (dt, 2, J = 2.7, 6.9), 2.84 (t, 2, J = 7.6), 4.25 (m, 1), 5.98 (s, 1); ^{13}C NMR δ 10.44, 13.80, 16.65, 19.59, 23.23, 26.28, 26.88, 31.08, 39.12, 47.02, 77.51, 79.26, 102.70, 104.33, 104.66, 111.72, 154.38, 156.73, 157.60, 160.12, 161.90, 190.09; MS (EI) *m/z* (rel. int.) 370 (62), 314 (100), 286 (85), 259 (42), 230 (31), 215 (25), 202 (33); IR cm^{-1} 3005, 1720, 1605, 1582, 1554, 1445, 1372, 1313, 1227, 1201, 1152, 1125. Anal. Calcd. for $C_{22}H_{26}O_5 \cdot 1/4\ H_2O$: C, 70.47; H, 7.12. Found: C, 70.54; H, 7.07. *cis*-**19**: R_f 0.07 (5:2 hexane-EtOAc); mp 136-138 °C; ^{1}H NMR δ 1.01 (t, 3, J = 7.3), 1.15 (d, 3, J = 7.2), 1.41 (d, 3, J = 6.5), 1.43

(s, 6), 1.60 (m, 2), 1.85 (t, 2, J = 6.9), 2.66 (m, 3), 4.70 (dq, 1, J = 3.4, 6.5), 6.01 (s, 1); ^{13}C NMR δ 9.19, 13.82, 16.05, 16.73, 23.25, 26.66, 31.12, 39.15, 45.75, 76.93, 77.26, 102.15, 104.41, 104.74, 111.78, 154.68, 156.85, 157.61, 160.15, 161.74, 191.75; MS (EI) *m/z* (rel. int.) 370 (62), 314 (100), 286 (78), 259 (43), 230 (30), 215 (26), 202 (33); IR cm^{-1} 2960, 1710, 1608, 1580, 1555, 1454, 1422, 1385, 1199, 1157, 1117. Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.09. Found: C, 71.12; H, 7.16.

***trans* and *cis*-4-Propyl-10,11-dihydro-6,6,10,11-tetramethyl-2*H*,6*H*,12*H*-benzo[1,2-b:3,4-b':5,6-b'']tripyran-2,12-dione (21) and (20).** A solution of *trans*-**19** (0.050 g, 0.13 mmol), NBS (0.030 g, 0.17 mmol), and AIBN (approximately 1 mg) in anhydrous CCl_4 (5.0 mL) was refluxed 45 min, then cooled, filtered, and the solvent removed *in vacuo*. The crude product was dissolved in NH_4Cl saturated MeOH (5.0 mL), zinc dust (0.050 g, 0.76 mmol) added, and the reaction refluxed 90 min. The solution was cooled, diluted with H_2O, and extracted with Et_2O. Flash chromatography (5:2 hexane-EtOAc) gave **21** (0.017 g, 35% yield) and **20** (0.019 g, 39% yield): **21**: R_f 0.17 (2:1 hexane-EtOAc); mp 170-171 °C (Lit.[3a] mp 130-132 °C; ^{1}H NMR δ 1.03 (t, 3, J = 7.3), 1.21 (d, 3, J = 6.9), 1.52 (d, 3, J = 6.2), 1.55 (s, 6), 1.64 (m , 2), 2.55 (dq, 1, J = 6.9, 11.1), 2.88 (m, 2), 4.30 (dq, 1, J = 6.2, 11.1), 5.60 (d, 1, J = 10.1), 6.04 (s, 1), 6.65 (d, 1, J = 10.1); ^{13}C NMR δ 10.31, 13.80, 19.49, 23.03, 27.82. 28.16, 38.62, 47.11, 79.13, 79.40, 103.32, 104.23, 105.38, 111.80, 115.67, 126.90, 155.31, 155.80, 157.01, 158.96, 159.60, 189.65; MS (EI) *m/z* (rel. int.) 368 (35), 353 (100), 297 (67), 269 (25), 241 (9); IR cm^{-1} 2965, 1735, 1681, 1608, 1577, 1458, 1384, 1335, 1152, 1113. Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72%; H, 6.57%. Found: C, 71.56%; H, 6.64%. **20**: R_f 0.13 (2:1 hexane-EtOAc); ^{1}H NMR δ 0.95 (t, 3, J = 7.3), 1.08 (d, 3, J =

7.2), 1.34 (d, 3, J = 6.6), 1.46 (s, 3), 1.48 (s, 3), 1.55 (m, 2), 2.60 (dq, 1, J = 3.4, 7.2), 2.80 (m, 2), 4.64 (dq, 1, J = 3.4, 6.6), 5.53 (d, 1, J = 10.1), 5.96 (s, 1), 6.58 (d, 1, J = 10.1); ^{13}C NMR δ 9.14, 13.83, 15.95, 23.08, 27.74, 28.18, 38.68, 45.83, 77.10, 79.24, 102.78, 104.34, 105.47, 111.87, 115.73, 126.93, 155.65, 155.98, 157.14, 158.83, 159.75, 191.56; MS (EI) *m/z* (rel. int.) 368 (33), 353 (100), 297 (66), 269 (26), 241 (10); IR cm^{-1} 2965, 1730, 1681, 1608, 1575, 1456, 1380, 1337, 1120. Anal. Calcd. for $C_{22}H_{24}O_5 \cdot 1/2\ H_2O$: C, 70.01; H, 6.68. Found: C, 70.04; H, 6.63.

(±)-Calanolide A (1). $NaBH_4$ (0.5 M in 2-methoxyethyl ether; 0.50 mL, 0.25 mmol) was added to a solution of **21** (0.041 g, 0.11 mmol) and $CeCl_3 \cdot 7\ (H_2O)$ (0.049 g, 0.13 mmol) in MeOH (10.0 mL). The reaction was stirred 30 min, then quenched with saturated aqueous NH_4Cl and extracted with Et_2O. Flash chromatography (4:1 hexane-EtOAc) gave **1** (0.037 g, 89%): R_f 0.22 (2:1 hexane-EtOAc); ^{1}H NMR δ 1.03 (t, 3, J = 7.4), 1.15 (d, 3, J = 6.8), 1.46 (s, 3), 1.46 (d, 3, J = 6.4), 1.51 (s, 3), 1.64 (m, 2), 1.93 (m, 1), 2.88 (m, 2), 3.66 (d, 1, J = 3.2), 3.92 (dq, 1, J = 6.4, 9.0), 4.72 (dd, 1, J = 3.0, 7.8), 5.54 (d, 1, J = 10.0), 5.94 (s, 1), 6.62 (d, 1, J = 10.0); ^{13}C NMR δ 13.95, 15.08, 18.91, 23.23, 27.34, 27.98, 38.62, 40.41, 67.07, 77.12, 77.63, 104.01, 106.32, 106.37, 110.08, 116.49, 126.93, 151.10, 153.09, 154.46, 158.88, 160.51; MS (EI) *m/z* (rel. int.) 370 (25), 355 (100), 299 (66), 271 (18); IR cm^{-1} 3595, 2965, 1718, 1586, 1377, 1182, 1140, 1121, 1107. Anal. Calcd. for $C_{22}H_{26}O_5 \cdot 1/3\ H_2O$: C, 70.19; H, 7.14. Found: C, 69.96; H, 7.26.

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References

1. Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina II, J. H.; McMahon, J. B.; Currens, M. J.; Buckheit, R. W., Jr.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 2735.
2. Fuller, R. W.; Bokesch, H. R.; Gustafson, K. R.; McKee, T. C.; Cardellina II, J. H.; McMahon, J. B.; Cragg, G. M.; Soejarto, D. D.; Boyd, M. R. *Bioorg. & Med. Chem. Lett.* **1994**, *4*, 1961.
3. During the course of this work other syntheses of (±)-**1** were reported: (a) Chenera, B.; West, M. L.; Finkelstein, J. A.; Dreyer, G. B. *J. Org. Chem.* **1993**, *58*, 5605. (b) Palmer, C.; Josephs, J. L. *Tetrahedron Lett.* **1994**, *35*, 5363-5366. (c) Kucherenko, A.; Flavin, M. T.; Boulanger, W. A.; Khilevich, A.; Shone, R. L.; Rizzo, J. D.; Sheinkman, A. K.; Xu, Z.-Q. *Tetrahedron Lett.* **1995**, *36*, 5475. (d) Palmer, C. J.; Josephs, J. L. *J. Chem. Soc. Perkin Trans. 1* **1995**, 3135. (e) Flavin, M. T.; Rizzo, J. D.; Khilevich, A.; Kucherenko, A.; Sheinkman, A. K.; Vilaychack, V.; Lin, L.; Chen, W.; Greenwood, E. M.; Pengsuparp, T.; Pezzuto, J. M.; Hughes, S. H.; Flavin, T. M.; Cibulski, M.; Boulanger, W. A.; Shone, R. L.; Xu, Z.-Q. *J. Med. Chem.* **1996**, *39*, 1303. A chiral synthesis of **1** has also been reported: (f) Deshpande, P. P.; Tagliaferri, F.; Victory, S. F.; Yan, S.; Baker, D. C. *J. Org. Chem.* **1995**, *60*, 2964-2965.
4. Szell, T.; Dozsai, L.; Zarady, M.; Menyharth, K. *Tetrahedron* **1969**, *25*, 715.
5. Crombie, L.; Whiting, D. A.; Clarke, D. G. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1007.

6. Stout, G.H.; Stevens, K. L. *J. Org. Chem.* **1964**, *29*, 3604.
7. Buchi, G. Weinreb, S.; *J. Am. Chem. Soc.* **1971**, *93*, 746.
8. Attempts to cleanly effect the direct transformation of **14** to **16** were unsuccessful.
9. Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.
10. Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1.
11. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
12. Szell, T. *J. Chem. Soc. (C)* **1967**, 2041.

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