A Simple Approach to the Synthesis of the Chiral Substituted Chroman Ring of Calophyllum Coumarins

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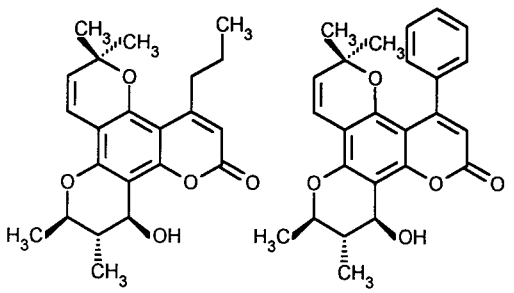
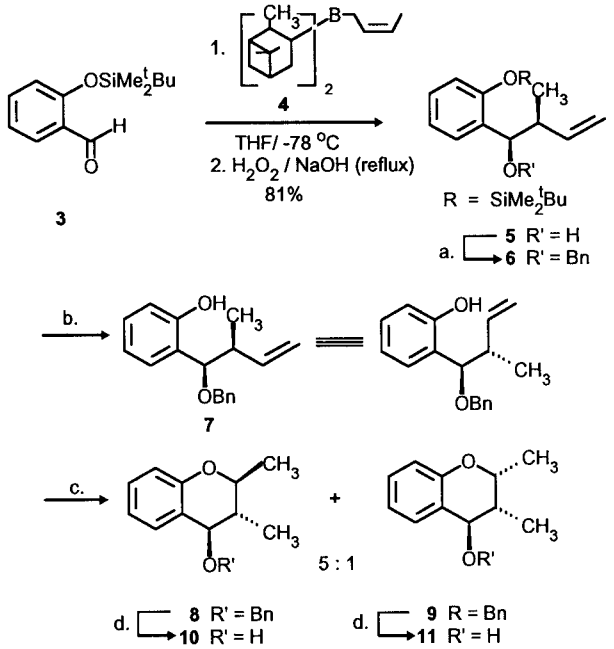
A stereoselective synthesis of the chiral 2,3-dimethylchroman-4-ol ring of the calophyllum coumarins is described. The chiral centers at C-3 and C-4 (chroman numbering) were introduced using (*Z*)-crotyldiisopinocampheylborane, and the chiral center at C-2 was introduced via mercury-assisted cyclization and demercuration, giving the required *trans, trans*-Me–Me–OH substituted chroman (benzo[*b*]pyran) ring.

The calanolides[1] and inophyllums[2–4] belong to a class of substituted coumarins isolated from the tropical rain forest trees, *Calophyllum lanigerum* and *inophyllum*, respectively. Recently it was discovered that calanolide A[1] **(1)** and inophyllum B[4] **(2)** have potent inhibitory activity towards human immunodeficiency virus-1 (HIV-1) reverse transcriptase. These novel non-nucleoside inhibitors, which have a distinctly different mechanism of action with the reverse transcriptase,[5] are interesting chemical structures based on phloroglucinol as the core of the system.[6] The common structural features of **1** and **2** include a chromene ring, a coumarin ring, and, most essential for their activity, a 2,3-dimethylchroman-4-ol (3,4-dihydro-2*H*-benzo[*b*]pyran system) bearing methyl groups at C-2 and C-3 in a trans relationship, and a hydroxy group at C-4 (chroman numbering). A synthesis of racemic calanolides has been reported by Dreyer and co-workers,[6] as well as by Palmer and Josephs.[7] While their approaches were an improvement over the earlier synthesis of dihydroinophyllolide[8] and dihydrocostatolide[9] reported by Polonsky and co-workers[8] and Stout and Stevens,[9] respectively, a total synthesis of these optically active coumarins remains to be achieved. The only method reported for an enantioselective synthesis of the substituted chromanol ring systems found in the calophyllum coumarin-type compounds is that of Rao et al.[10] who used a Houben–Hoesch reaction to install one of three chiral centers, which upon further methylation gave a mixture of *cis*- and *trans*-dimethyl chromanones (in ca. 1:1 ratio) that were separated by chromatography. The chromanone was then reduced with sodium borohydride–cerium(III) chloride to give the chromanol with > 95% diastereoselectivity. Herein we report a unique entry into the requisite fused pyran (chroman) system related to **1** and **2** that provides in high enantiomeric yield the contiguous *trans,trans*-Me–Me–OH group set of substituents.

The synthesis of the 2,3-dimethylchroman-4-ols was carried out as shown in the Scheme. 2-(*tert*-Butyldimethylsilyloxy)benzaldehyde **(3)**[11] was converted into the enantiomerically pure *erythro*-β-methylhomoallylic alcohol **5** in greater than 94% ee[12] by reaction with (*Z*)-crotyldiisopinocampheylborane **(4)**.[13] The relative and absolute stereochemistries were assigned, first by analogy with the results for the homoallylic alcohols prepared by Brown and Bhat,[13] and then by the ^{1}H NMR method of Kakisawa and co-workers.[14] Benzylation of the homoallylic alcohol **5** was carried out in the presence of silver oxide and benzyl bromide in CH_2Cl_2 for 48 hours to obtain **6**, isolated in 97% yield as a syrup that was characterized by its ^{1}H and ^{13}C NMR spectra. Desilylation of **6** with tetrabutylammonium fluoride afforded the corresponding phenol **7** in 94% yield, which was fully characterized by NMR spectroscopy and elemental analysis. The cyclization of the *ortho*-alkenylphenol[15] **7** was carried out with mercuric acetate[16] in tetrahydrofuran. The intermediate organomercurial was then reduced with sodium borohydride to obtain inseparable fused-ring dihydropy-





Reagents: a. Ag_2O/BnBr/CH_2Cl_2; b. Bu_4NF/DMF; c. (1) $Hg(OAc)_2$/THF (dark), (2) $NaBH_4$/NaOH; d. $Pd(OH)_2$/EtOH/cyclohexene (reflux).

Scheme

rans **8** and **9** (5:1 ratio by ^{1}H NMR spectroscopy) in 64% yield. Debenzylation of **8** and **9** proceeded smoothly by catalytic-transfer hydrogenation[17] to give the required 2,3-dimethylchroman-4-ols **10** (56) and **11** (12%), which were easily separated by silica gel column chromatography. Compounds **10** and **11** were distinguished from one another principally via the resonances observed for H-2. The H-2 resonance appears at lower field for the *cis*-dimethyl compound **11**, which is in accord with observations made for similar systems.[4,10] The precise spin–spin splittings were, unfortunately, difficult to discern at 250 MHz (H-2 and H-4 overlap in **11**).

The abovementioned approach provides a relatively easy access to the chiral 2,3-dimethylchroman-4-ol system of calanolides having a *trans,trans*-Me–Me–OH relationship. The key step in the sequence is to obtain the *erythro*-β-methylhomoallylic alcohols such as **5** in both a regio- and stereoselective manner on a substrate that is more complex than those used in the development of these types of reactions.[13] The application of this process to the preparation of the optically active calanolides is now under intensive investigation.

Analytical TLC was performed on aluminum-backed plates coated with E. Merck Silica Gel-60 F-254. The developed plates were air dried and irradiated with UV light and/or dipped in a mixture of *p*-anisaldehyde, AcOH, and sulfuric acid in EtOH, and heated at 120–140 °C.[18] Flash column chromatography was performed on Silica Gel-60 (230–400 mesh). The solvent systems used were: A, 8:2 hexanes–EtOAc; and B, 8:2 $CHCl_3$–hexanes. Optical rotations were measured with a Perkin-Elmer Model 243 automatic polarimeter for solutions in a 0.1 dm cell at the indicated temperature. IR spectra were recorded with a Perkin-Elmer spectrophotometer, model 710B. Routine ^{1}H and ^{13}C NMR spectra were recorded at 250 MHz and 62.5 MHz, respectively, on a Bruker AM 250 instrument using $CDCl_3$ as the solvent and Me_4Si as the internal standard. Chemical shifts and coupling constants were obtained from a first-order analysis of the spectra. The mass spectrum was obtained on a VG-ZAB instrument in the electron-impact mode. Compounds **5**, **7**, **8** and **9** (5:1 mixture), and **10** gave C, H analysis ± 0.16%.

(1*R*,2*S*)-1-(2-*tert*-Butyldimethylsilyloxyphenyl)-2-methylbut-3-en-1-ol (5):

The organoborane reagent **4** was prepared according to the procedure of Brown and Bhat.[13] To a stirred mixture of *t*-BuOK (638 mg, 5.68 mmol), THF (4 mL) and *cis*-2-butene (4 mL, 44.44 mmol) was added BuLi (2.5 M in hexane) (2.27 mL, 5.68 mmol) at −78 °C. After completion of the addition of BuLi, the mixture was allowed to warm to −45 °C for 10 min, then it was recooled to −78 °C, at which point (−)-β-methoxydiisopinocampheylborane (1.91 g, 6.06 mmol) in THF (3 mL) was added. The reaction mixture was stirred at −78 °C for 30 min, $BF_3 \cdot Et_2O$ (0.79 mL, 1.79 equiv) was added dropwise, and compound **3**[11] (900 mg, 3.79 mmol) in THF was then added at −78 °C. The mixture was stirred at −78 °C for 3 h, then treated with 3 N NaOH (10 mL) and 30% H_2O_2 (8 mL) and refluxed for 1 h. The organic layer was separated, washed with water (15 mL) and brine (10 mL), dried ($MgSO_4$), concentrated and submitted to flash chromatography (solvent B) to obtain **5** [900 mg, 81% (with 94% diastereoselectivity and 94% enantioselectivity)[12]] as an oil: $[\alpha]_D^{25}$ −19.0° (*c* = 1.0, $CHCl_3$).

IR (film): ν = 3400, 3050, 2900, 1590, 1570, 1470, 1440, 1240, 1000, 820, 700 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.26 (s, 3H, $SiCH_3$), 0.30 (s, 3H, $SiCH_3$), 1.0 (d, 3H, *J* = 7.0 Hz, CH_3), 1.03 (s, 9H, $-CMe_3$), 2.10 (br s, 1H, OH), 2.68 (m, 1H, C*H*CH_3), 4.95 (d, 1H, *J* = 5.15 Hz, C*H*OH), 5.02 (d, 1H, *J* = 1.24 Hz, CH=CH_2), 5.08 (m, 1H, CH=CH_2), 5.87 (m, 1H, C*H*=CH_2), 6.79 (d, 1H, *J* = 7.92 Hz, ArH), 6.95 (t, 1H, *J* = 6.55 Hz, ArH), 7.13 (t, 1H, *J* = 7.76 Hz, ArH), 7.36 (d, 1H, *J* = 7.55 Hz, ArH).

^{13}C NMR: δ = −1.55, −1.17, 13.15, 18.24, 25.87, 42.66, 72.22, 114.89, 117.98, 120.81, 127.78, 127.93, 132.96, 141.21, 152.40.

(1*R*,2*S*)-2-(1-Benzyloxy-2-methylbut-3-enyl)-1-(*tert*-butyldimethylsilyloxy)benzene (6):

To a solution of **5** (400 mg, 1.37 mmol) in CH_2Cl_2 (30 mL) was added $PhCH_2Br$ (700 mg, 4.10 mmol) and Ag_2O (950 mg, 4.10 mmol). The reaction mixture was stirred for 24 h, and then filtered through Celite 545. To the filtrate was added fresh Ag_2O (950 mg, 4.10 mmol), and the reaction mixture was stirred for a further 24 h, then filtered through Celite 545, concentrated, and purified by flash chromatography (solvent B) to obtain **6** (510 mg, 97%) as a syrup: $[\alpha]_D^{25}$ −22.0° (*c* = 1.0, $CHCl_3$).

IR (film): ν = 3075, 3025, 2950, 2860, 2630, 1600, 1585, 1490, 1450, 1400, 1360, 1260, 1100, 1060, 1000, 920, 840 cm^{-1}.

^{1}H NMR: δ = 0.20 (s, 3H, CH_3), 0.25 (s, 3H, CH_3), 0.96 (s, 9H, CMe_3), 1.06 (d, 3H, *J* = 6.7 Hz, CHCH_3), 2.55 (m, 1H, C*H*CH_3), 4.24 and 4.26 (2 d, 2H, *J* = 11.65 Hz, $-CH_2Ar$), 4.76 (d, 1H, *J* = 5.5 Hz, $-CH$OBn), 4.88–4.97 (m, 2H, CH=CH_2), 5.84 (m, 1H, C*H*=CH_2), 6.79 (d, 1H, *J* = 7.98 Hz, ArH), 6.97 (br t, 1H, *J* = 7.32 Hz, ArH), 7.14 (br t, 1H, *J* = 6.23, ArH), 7.40 (m, 5H, CH_2ArH), 7.42 (d, 1H, *J* = 6.36 Hz, ArH).

^{13}C NMR: δ = −1.49, −1.21, 14.68, 18.24, 25.86, 43.35, 70.68, 78.29, 113.95, 117.90, 120.87, 127.26, 127.54, 127.78, 128.18, 131.21, 138.99, 141.49, 153.64.

MS: *m*/*z* = 327 [M^+ − 55 ($CH_3CHCH=CH_2$)].

(1*R*,2*S*)-2-(1-Benzyloxy-2-methylbut-3-enyl)phenol (7):

To a solution of **6** (350 mg, 0.914 mmol) in THF (10 mL) was added dropwise tetrabutylammonium fluoride (1 M solution in THF, 1.09 mL, 1.09 mmol). After 1 h the reaction mixture was poured into water (5 mL), and the product was extracted with Et_2O (3 × 5 mL). The ethereal layers were washed with brine (2 × 2 mL), dried ($MgSO_4$), concentrated, and then submitted to flash chromatography to give **7** (231 mg in 94%) as a syrup: $[\alpha]_D^{25}$ −3.0° (*c* = 1.0, $CHCl_3$).

IR (film): ν = 3350, 3000, 2900, 2850, 1610, 1580, 1480, 1440, 1380, 1230, 1040, 1020, 910, 740 cm^{-1}.

^{1}H NMR: δ = 1.13 (d, 3H, *J* = 6.71 Hz, CHCH_3), 2.69 (m, 1H, C*H*CH_3), 4.24 (d, 1H, *J* = 7.27 Hz, C*H*OBn), 4.40 and 4.64 (2d, 2H, *J* = 11.44 Hz, CH_2Ar), 4.89 (s, 1H, CH=CH_2), 4.94 (br d, 1H, *J* = 6.7 Hz, CH=CH_2), 5.60 (m, 1H, C*H*=CH_2), 6.80–7.40 (m, 9H, ArH), 7.93 (s, 1H, OH).

^{13}C NMR: δ = 16.09, 43.05, 71.76, 87.17, 115.32, 116.86, 119.41, 128.08, 128.27, 128.48, 129.11, 129.67, 136.90, 139.86, 155.69.

(2*S*,3*R*,4*R*)-4-Benzyloxy-2,3-dimethylbenzo[*b*]pyran (8) and (2*R*,3*R*,4*R*)-Benzyloxy-2,3-dimethylbenzo[*b*]pyran (9):

To a solution of **7** (200 mg, 0.745 mmol) in dry THF (6 mL) was added mercuric acetate (712 mg, 2.23 mmol), and the mixture was stirred for 20 h in the dark. The organomercurial thus formed was treated with sodium borohydride (281 mg, 7.45 mmol) and 3 N aq NaOH (2 mL), and the mixture was stirred for 2 h. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (2 × 3 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography (solvent B) to obtain **8** and **9** as an inseparable mixture (5:1 mixture of **8** and **9**, respectively, by ^{1}H NMR) (128 mg, 64%) as a syrup. Data is given for compounds **8** and **9** (5:1 mixture).

IR (film): ν = 3000, 2950, 2900, 1600, 1580, 1480, 1440, 1380, 1220, 1060, 920, 740 cm^{-1}.

^{1}H NMR (* indicates discernable resonances for **9**): δ = 1.12 (d, 3H, *J* = 6.48 Hz, CH_3), 1.43 (d, 3H, 6.48 Hz, CH_2), 2.15 (m, 1H, H-3), 2.45* (m, H-3), 3.95 (m, 1H, H-2), 4.30* (m, H-2), 4.40–4.60 (m, 3H, H-4, CH_2Ar), 6.7–7.5 (m, 9H, ArH).

^{13}C NMR: δ = 14.36, 19.40, 37.05, 68.31, 76.44, 78.01, 116.53, 120.47, 127.69, 127.74, 127.93, 128.42, 128.90, 131.90, 138.55.

(2*S*,3*R*,4*R*)-2,3-Dimethylbenzo[*b*]pyran-4-ol (10) and (2*R*,3*R*,4*R*)-2,3-Dimethylbenzo[*b*]pyran-4-ol (11):
To a solution of **8** and **9** (60 mg, 0.22 mmol) in abs. ethanol (4 mL) was added $Pd(OH)_2$ (10 mg) and cyclohexene (3 mL). The mixture was refluxed for 5 h, the catalyst was filtered off, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (solvent A) to obtain **10** (22 mg) and **11** (5 mg) [27 mg (72%) combined yield].

Compound **10**:

White solid, mp 92–93 °C; $[\alpha]_D^{25}$ −81.0° (c = 1.0, $CHCl_3$).

IR (Nujol): ν = 3200, 2740, 1590, 1255, 1015, 810 cm^{-1}.

^1H NMR: δ = 1.13 (d, 3H, J = 6.55 Hz, CH_3), 1.40 (d, 3H, J = 6.22 Hz, CH_3), 1.57 (br s, 1H, OH), 1.70 (m, 1H, H-3), 3.95 (m, 1H, H-2), 4.37 (d, 1H, J = 9.76, H-4), 6.8 (d, 1H, J = 7.5 Hz, ArH), 6.93 (t, 1H, J = 7.40 Hz, ArH), 7.16 (t, 1H, J = 7.22 Hz, ArH), 7.46 (d, 1H, J = 7.60 Hz, ArH).

^{13}C NMR: δ = 14.09, 19.25, 42.36, 71.42, 76.16, 116.23, 120.60, 127.20, 128.45, 128.93, 129.47.

Compound **11**:

White solid, mp 102–103°C; $[\alpha]_D^{25}$ −16.0° (c = 1.0, $CHCl_3$).

^1H NMR: δ = 0.81 (d, 1H, J = 7.26 Hz, CH_3), 1.40 (d, 1H, J = 6.64 Hz, CH_3), 1.55 (br s, 1H, OH), 1.95 (m, 1H, H-3), 4.45 (m, 2H, H-2, H-4), 6.80–7.40 (m, 4H, ArH).

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