Synthesis of Schumanniophytine and Isoschumanniophytine

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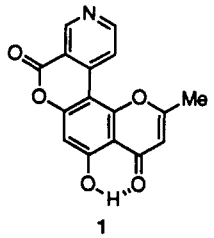
Some controversy has surrounded the structures of the *Schumanniophyton* alkaloids schumanniophytine and isoschumanniophytine. In 1978 Schlittler and Spitaler described[1] the isolation of an alkaloid which they named schumanniophytine and to which they assigned structure **1**. In 1985 Houghton and Yang reported[2] the isolation of schumanniophytine from a different source but, although cognizant of the earlier work, assigned it structure **2**. Houghton and Yang also isolated an isomer of schumanniophytine, named it isoschumanniophytine, and assigned it structure **3**, in part because schumanniophytine and isoschumanniophytine are each converted to a mixture of the two by treatment with NaOH in refluxing ethanol followed by an acidic workup. The interconversion of **2** and **3** can be accounted for straightforwardly by opening of the lactone rings followed by closure to give either **2** or **3**.



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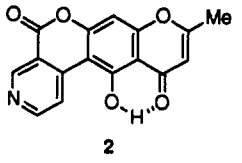

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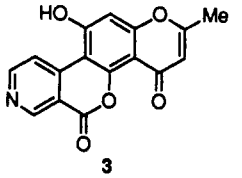

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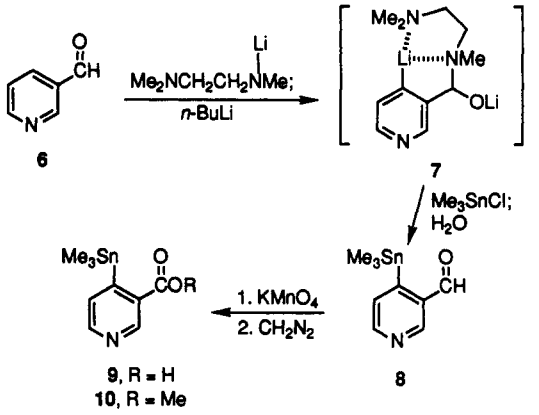
In 1987 Houghton[3] revised his earlier structure designations, changing the structure of schumanniophytine to **1** (thereby concurring with Schlittler and Spitaler) and of isoschumanniophytine to **2**. The above-mentioned interconversion of schummaniophytine and isoschummaniophytine is less easily accommodated by structures **1** and **2** but can be envisaged to occur by scission (and reassembly) of both the α- and γ-pyrone rings. To date, no synthetic or X-ray crystallographic studies relating to structures **1–3** have been recorded.

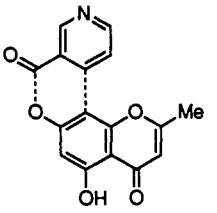
Structures **1–3** are representatives of the rare tetracyclic pyranobenzopyranopyridine family of ring systems. The history of uncertainty surrounding the structures of schumanniophytine and isoschumanniophytine, the novelty of the heteroaromatic nuclei, and the dearth[4] of previous synthetic activity in this area led us to undertake syntheses of **1** and **2**. As we now report, these efforts

Scheme I



establish that structures **1** and **2** are, in fact, the correct structures of schumanniophytine and isoschumanniophytine, respectively.

Retrosynthetic analysis, guided by considerations of economy, suggested that despite their differences, both **1** and **2** might be produced from essentially the same precursors: a nicotinic acid derivative and a dihydroxychromone-based unit, as indicated in **4** and **5**. It was hoped that the biaryl bonds in **1** and **2** could be formed by palladium-catalyzed coupling reactions.[5]



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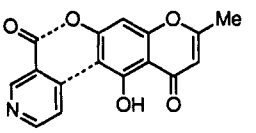

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The nicotinic acid derivative **10** is common to the synthesis of both **1** and **2**. It was prepared as indicated in Scheme I, using the Comins[6] method for regiospecific[7] lithiation of nicotinaldehyde (**6**) at the 4-position to give **8** in 60% overall yield from **6**. Oxidation[8] and reaction with diazomethane then provided ester **10**.

Bromination of the known[9] chromone benzyl ether **11** proceeds (eq 1) with little regioselectivity to give **12** and **13**. This lack of regioselectivity is an advantage in the present instance, since both regioisomers are required for the syntheses. The ^{1}H NMR spectra of **12** and **13** are quite similar and do not allow for conclusive determination of structure. Structural assignment was achieved, instead, by conversion of one of the regioisomers (**12**) to its methyl ether (**14**) and chemical correlation with known[10] iodochromone **16** by the reactions indicated in eq 2. Further confirmation of the regiochemistry assigned to **12** and **13** was obtained by NOE experiments on the corresponding methyl ethers **14** and **15**. Irradiation of the methoxy protons in **14** gave a 16% enhancement of the resonance

(1) Schlittler, E.; Spitaler, U. *Tetrahedron Lett.* **1978**, 2911–2914.
(2) Houghton, P. J.; Yang, H. *Planta Med.* **1985**, 23–27.
(3) Houghton, P. J. *Planta Med.* **1987**, 264–266.
(4) For the few available examples of syntheses of any types of molecules containing pyranobenzopyranopyridine skeletons, see: Reisch, J.; Mester, I.; Aly, S. M. *J. Chem. Soc., Perkin Trans. 1*, **1983**, 219–223. Reisch, J.; Aly, S. M. E. *Arch. Pharm. (Weinheim, Ger.)* **1986**, *319*, 25–28. Hishmat, O. H.; El-Ebrashi, N. M. A.; El Naem, S. E.; Abd El Rahman, A. H. *Synthesis* **1982**, 1075–1077. Hishmat, O. H.; Khalil, K. H. M.; Abdel Galil, F. M.; El-Naem, S. E.; Magd-el-Din, A. A. *Pharmazie* **1989**, *44*, 793–794 and references therein.
(5) Cf. Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977–991.
(6) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69–73.
(7) Preferential lithiation at the 4 (rather than the 2) position was expected. See, inter alia, ref 5 and the following. Gungor, T.; Marsais, F.; Queguiner, G. *Synthesis* **1982**, 499–500. Epsztajn, J.; Brzezinski, J. C.; Jozwiak, A. *J. Chem. Res.* **1986**, 18–19 and references therein.
(8) Weber, E.; Czugler, M.; Csoregh, I.; Stensland, B. *J. Am. Chem. Soc.* **1984**, *106*, 3297–3306.
(9) Gulati, K. C.; Seth, S. R.; Venkataraman, K. *J. Chem. Soc.* **1934**, *127*, 1765–1767. See also: Bolleter, A.; Eiter, K.; Schmid, H. *Helv. Chim. Acta* **1951**, *34*, 186–194.
(10) Ahluwalia, V. K.; Jain, A.; Gupta, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2649–2652.

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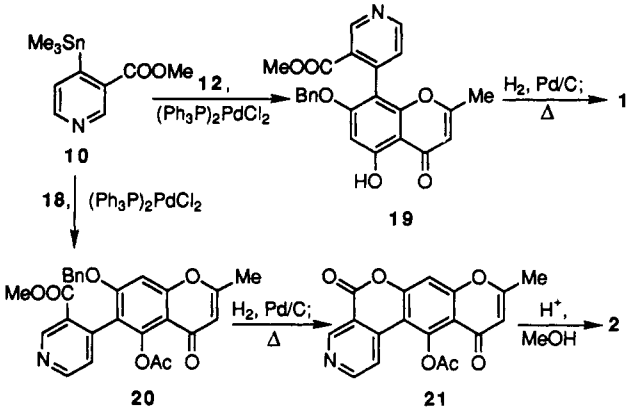
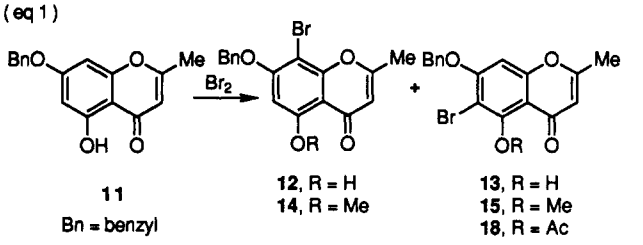
Scheme II

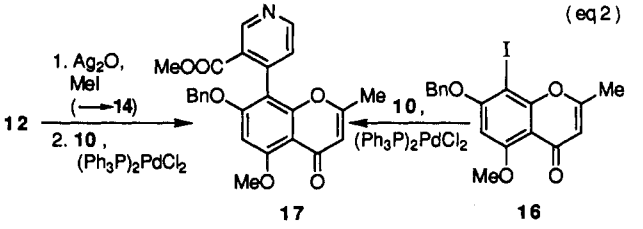


of the adjacent aryl-H proton; irradiation of the methoxy protons in **15** led to no enhancement of the aryl-H resonance. For reasons discussed below, bromochromone **13** was employed as its acetate **18** in subsequent reactions.

(eq 1)

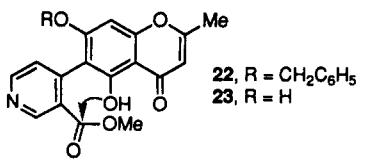


(eq 2)



As anticipated, owing to the presence of three ortho (including two electron donating) substituents, coupling of **10** with **12** and **18** proved difficult,[5] but the desired products were nonetheless secured in due course (Scheme II). Conversion of **19**, the coupling product of **10** and **12**, to **1** was straightforward: hydrogenolysis of the benzyl group was followed, upon heating, by lactonization, to give **1** directly. Spectral data for synthetic **1** agree with those reported for natural schumanniophytine and direct comparison of synthetic **1** and natural **1** (i.e. schumanniophytine) confirm the identity.

For the coupling of **10** with **13**, the free OH group in **13** was first acetylated[11] (→**18**) to ensure that possible lactonization of the ester onto the "wrong" OH in **22** (or in the debenzylated derivative **23**) would not derail the synthesis. Coupling of **10** with **18** (Scheme II) then afforded **20**. Hydrogenolytic debenzylation of **20** was again followed by lactonization, giving **21**. Methanolysis of **21** then furnished **2**, whose spectra are identical to those reported for isoschumanniophytine. Direct comparison of synthetic **2** with natural isoschumanniophytine affirmed their identity.



(11) Illi, V. O. *Tetrahedron Lett.* **1979**, 2431–2432.

Conclusion

The present work confirms the assignment of structures **1** and **2** to schumanniophytine and isoschumanniophytine, respectively. It also provides convergent syntheses wherein the longest sequence from commercial material to tetracyclic target is six steps to **1** and eight steps to **2**.

Experimental Section[12]

4-(Trimethylstannyl)-3-pyridinecarboxaldehyde (8). To a stirred solution of *N,N,N'*-trimethylethylenediamine (6.12 mL, 48.0 mmol) in dry THF (150 mL) was added *n*-butyllithium (17.6 mL of a 2.5 M solution in hexanes, 44.0 mmol; Aldrich) at −78 °C, and the mixture was stirred at that temperature for 15 min under nitrogen. To the reaction solution was added 3-pyridinecarboxaldehyde (**6**; Aldrich; 3.80 mL, 40.0 mmol) in one portion, and the solution was stirred at −78 °C for 15 min. After the solution was warmed to −42 °C, *n*-butyllithium (32.0 mL of a 2.5 M solution in hexanes, 80 mmol) was added in one portion, and the mixture was stirred at −42 °C for 3 h. After cooling to −78 °C, trimethyltin chloride (16.7 g, 83.9 mmol) in dry THF (100 mL) was added over a couple of minutes, and the cold bath was removed; the reaction mixture was stirred for 2–3 h (during which time it came to room temperature). The reaction was quenched with cold brine (200 mL) and extracted with diethyl ether (3 × 300 mL). The organic phase was dried (K_2CO_3) and evaporated. The residue was separated by flash column chromatography on a 2-in. × 14-in. column, eluting with 3:2 petroleum ether/ethyl acetate to give **8** (6.43 g, 23.8 mmol, 60%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.32 (9 H, s), 7.67 (1 H, dd, J = 4.5, 0.9 Hz), 8.71 (1 H, d, J = 4.5 Hz) 8.98 (1 H, s), 10.10 (1 H, d, J = 0.9 Hz); MS m/z (rel intensity) 270 (4, M^+), 256 (42), 255 (19), 254 (35), 253 (13), 252 (21), 57 (100); IR (neat) ν 2973, 2917, 2840, 2741, 1708, 1687, 1574, 1525 cm^{-1}. Anal. Calcd for $C_9H_{13}NOSn$: C, 40.05; H, 4.86; N, 5.19. Found: C, 40.30; H, 4.75; N, 4.95.

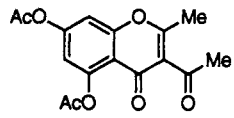
4-(Trimethylstannyl)-3-pyridinecarboxylic Acid (9). To a stirred solution of 4-(trimethylstannyl)-3-pyridinecarboxaldehyde (**8**; 6.39 g, 23.7 mmol) in acetone (160 mL) was added a solution of $KMnO_4$ (7.48 g, 47.3 mmol) in 1:1 acetone/H_2O (450 mL) through a dropping funnel at room temperature over 40 min. After being stirred for 2 h at room temperature, the reaction mixture was filtered through Celite. Ethanol (30 mL) was added to the filtrate followed by heating on the steam bath until (ca. 30 min) a clear colorless supernatant solution with a dark brown precipitate was obtained. After cooling, the MnO_2 precipitate was removed by filtration through Celite to give a clear filtrate. The filtrate was acidified to pH 3 with concentrated hydrochloric acid. The resulting solution was saturated with sodium chloride and extracted with ethyl acetate (5 × 150 mL). The combined extracts were dried (Na_2SO_4) and evaporated to give **9** (5.84 g, 20.4 mmol, 86%) as a white solid which was ordinarily used without further purification. Recrystallization of a sample from ethanol gave white crystals: mp 303–305 °C dec; ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 0.28 (9 H, s), 7.61 (1 H, d, J = 4.8 Hz), 8.62 (1 H, d, J = 4.8 Hz), 9.19 (1 H, s); MS m/z (rel intensity) 272 (100), 271 (33), 270 (74), 269 (28), 268 (45); IR (Nujol) ν 2460 (br), 1638, 1602, 1567, 1412 cm^{-1}.

Methyl 4-(Trimethylstannyl)-3-pyridinecarboxylate (10). To a solution of 4-(trimethylstannyl)-3-pyridinecarboxylic acid (**9**; 5.51 g, 19.3 mmol) in methanol (250 mL) at 0 °C was added excess ethereal diazomethane (from[13] *N*-nitrosomethylurea) in portions with swirling. After 10 min, the reaction mixture was evaporated on a steam bath to one-quarter of its original volume. The residue was diluted with dichloromethane (300 mL) and washed with brine (200 mL). The organic phase was dried (Na_2SO_4) and evaporated. The residue was separated by flash column chromatography on a 2-in. × 14-in. column, eluting with 1:1 Et_2O/petroleum ether to give **10** (3.46 g, 11.5 mmol, 60%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.31 (9 H, s), 3.96 (3 H, s),

(12) For general experimental procedures, see: Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024–8034. In all cases $CHCl_3$ was used as received (which means that the ~0.75% ethanol stabilizer was not removed).

(13) Arndt, F.; Noller, C. R.; Bergsteinsson, I. In *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, pp 165–167 (see note 3 therein).

7.60 (1 H, dd, J = 4.8, 0.9 Hz), 8.65 (1 H, d, J = 4.8 Hz), 9.23 (1 H, d, J = 0.9 Hz); MS m/z (rel intensity) 286 (100), 285 (35), 284 (76), 283 (28), 282 (44); IR (Nujol) ν 1735, 1567, 1532, 1398, 1293 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_2Sn$: C, 40.04; H, 5.05; N, 4.67. Found: C, 40.38; H, 5.30; N, 4.76.



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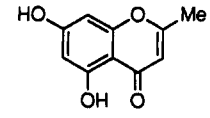

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3-Acetyl-5,7-bis(acetyloxy)-2-methyl-4*H*-1-benzopyran-4-one (24). The following procedure is a modification of one by Venkataraman et al.[9] To a stirred suspension of 2,4,6-trihydroxyacetophenone monohydrate (Aldrich; 24.9 g, 134 mmol) in acetic anhydride (400 mL, 4.24 mol) was added sodium acetate (25.1 g, 306 mmol). The reaction mixture was heated at reflux for 9 h with stirring. After cooling, excess acetic anhydride was removed in vacuo on a rotary evaporator. The residue was diluted with ethyl acetate (500 mL) and washed with H_2O (300 mL). The organic phase was dried (Na_2SO_4) and evaporated. The residue was purified by suction chromatography through a 5-in. × 5-in. pad of silica gel in a sintered-glass funnel, eluting with 5:1 diethyl ether/petroleum ether to eliminate polar impurities, and the eluate was evaporated to give an orange solid. The solid was suspended in petroleum ether and filtered to give **24** (41.8 g, 131 mmol, 98%) which was ordinarily used without further purification. Successive recrystallizations from ethanol, acetone/diethyl ether, and acetone gave **24** as yellow crystals: mp 128–130 °C (lit.[9] mp 130–131 °C); ^1H NMR ($CDCl_3$) δ 2.34 (3 H, s), 2.42 (3 H, s), 2.44 (3 H, s), 2.55 (3 H, s), 6.84 (1 H, d, J = 2.2 Hz), 7.20 (1 H, d, J = 2.2 Hz); MS m/z (rel intensity) 319 (18), 318 (M^+, 4), 227 (35), 276 (91), 234 (100); IR ($CHCl_3$) ν 1778, 1687, 1644, 1623, 1553, 1427, 1335 cm^{-1}.

5,7-Dihydroxy-2-methyl-4*H*-1-benzopyran-4-one (25). The following procedure is a modification of one by Venkataraman et al.[9] A stirred suspension of crude 3-acetyl-5,7-bis(acetyloxy)-2-methyl-4*H*-1-benzopyran-4-one (**24**; 41.8 g, 131 mmol) in 1 kg of 10% aqueous sodium carbonate was heated at reflux for 1 h. After cooling, the solid was filtered off and washed with H_2O (100 mL) to give a dark brown filtrate. The filtrate and wash were combined, neutralized to pH 7–8 with 2 N HCl (~300 mL), and cooled. The white solid that separated was collected by filtration and dried over P_2O_5 under vacuum in a desiccator for 16 h to give **25** (19.0 g, 98.7 mmol, 75%) as a white solid which was ordinarily used without further purification: mp 278–279 °C (lit.[9] mp 279–280 °C); ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.35 (3 H, s), 5.98 (1 H, s), 6.23 (1 H, d, J = 2.1 Hz), 6.31 (1 H, d, J = 2.1 Hz), 10.09 (1 H, br s), 12.69 (1 H, s); MS m/z (rel intensity) 192 (M^+, 100), 164 (67), 163 (45), 124 (24); IR (Nujol) ν 1659, 1623, 1567, 1504, 1349 cm^{-1}.

7-(Benzyloxy)-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (11). To a stirred solution of 5,7-dihydroxy-2-methyl-4*H*-1-benzopyran-4-one (**25**; 6.36 g, 33.1 mmol) in 3:1 (v:v) acetone/DMF (250 mL) was added freshly roasted[14] (over a Meker burner) potassium carbonate (6.86 g, 49.6 mmol) followed by benzyl bromide (5.51 mL, 46.3 mmol). The reaction mixture was stirred at room temperature for 16 h under nitrogen. The white solid was filtered off and washed with acetone. The combined filtrate and wash were concentrated in vacuo on a rotary evaporator, and the higher boiling contaminants were removed on a Kugelrohr distillation apparatus (~70 °C/1 Torr), giving a white-brown, solid residue. The solid was recrystallized from ethanol twice, giving **11** (6.09 g, 21.6 mmol, 65%) as a pale-yellow crystalline solid: mp 134–135 °C (lit.[9] mp 147–148 °C); ^1H NMR ($CDCl_3$) δ 2.32 (3 H, d, J = 0.7 Hz), 5.09 (2 H, s), 6.00 (1 H, q, J = 0.7 Hz), 6.40 (2 H, apparent d, J = 0.7 Hz), 7.40 (5 H, m), 12.71 (1 H, s); MS m/z (rel intensity) 282 (M^+, 73), 91 (100); IR ($CHCl_3$) ν 1666, 1623, 1588, 1504, 1441, 1420, 1391, 1335 cm^{-1}.

7-(Benzyloxy)-8-bromo-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (12) and 7-(Benzyloxy)-6-bromo-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (13). To a stirred solution of 7-(benzyloxy)-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (**11**, 4.79 g, 17.0 mmol) in $CHCl_3$ (200 mL) at 0 °C was added bromine (0.96 mL, 18.7 mmol) dropwise over ca. 10 min; the bromine drops decolorized immediately. The mixture was then left stirring for 20 min at room temperature. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (150 mL × 2), and the organic phase was dried ($MgSO_4$) and evaporated, giving a ~1:1 mixture (as judged by NMR) of the two regioisomers **12** and **13** (5.89 g, 16.3 mmol, 96%). Flash column chromatography on a 2-in. × 14-in. column, eluting with 1:1 $CHCl_3/C_6H_6$, gave first the less polar **12** (2.66 g, 7.36 mmol, 43%; mp 185–186 °C) and then a mixture of **12** and **13** followed by pure **13** (1.59 g, 4.40 mmol, 26%; mp 190–191 °C) as white solids. Rechromatography of the fractions containing mixtures of **12** and **13** gave additional material.

12: ^1H NMR ($CDCl_3$) δ 2.44 (3 H, d, J = 0.6 Hz), 5.22 (2 H, s), 6.08 (1 H, q, J = 0.6 Hz) 6.48 (1 H, s), 7.34 (5 H, m), 12.88 (1 H, s); MS m/z (rel intensity) 362 (40, M^+), 360 (41 M^+), 91 (100); IR (Nujol) ν 1659, 1623, 1595, 1405, 1328 cm^{-1}. An analytical sample was obtained as pale-yellow needles, mp 189–190 °C, after recrystallization from ethyl acetate. Anal. Calcd for $C_{17}H_{13}O_4Br$: C, 56.52; H, 3.63. Found: C, 56.52; H, 3.52.

13: ^1H NMR ($CDCl_3$) δ 2.36 (3 H, d, J = 0.9 Hz), 5.23 (2 H, s), 6.08 (1 H, q, J = 0.9 Hz), 6.47 (1 H, s), 7.41 (5 H, m), 13.43 (1 H, s); MS m/z (rel intensity) 362 (18, M^+), 360 (19, M^+), 281 (37), 91 (100); IR (Nujol) ν 1666, 1609, 1483, 1412, 1349, 1293 cm^{-1}. An analytical sample was obtained as white needles, mp 196–197 °C, after recrystallization from ethyl acetate. Anal. Calcd for $C_{17}H_{13}O_4Br$: C, 56.52; H, 3.63. Found: C, 56.47; H, 3.51.

7-(Benzyloxy)-8-bromo-5-methoxy-2-methyl-4*H*-1-benzopyran-4-one (14). To a solution of 7-(benzyloxy)-8-bromo-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (**12**; 51 mg, 0.14 mmol) in iodomethane (5 mL) was added 0.5 g of silver(I) oxide, and the reaction mixture was heated at reflux using a steam bath for 10 min. After cooling, the solid was filtered off and washed with CH_2Cl_2 (10 mL) to give a pale-purple mixture of filtrate and wash. The mixture was evaporated to give a pale-purple solid residue. The residue was separated by preparative TLC (1000-μm plate, 5:1 ethyl acetate/diethyl ether) to give **14** (44 mg, 0.12 mmol, 86%) as a white solid: ^1H NMR ($CDCl_3$) δ 2.36 (3 H, d, J = 0.6 Hz), 3.90 (3 H, s), 5.29 (2 H, s), 6.04 (1 H, q, J = 0.6 Hz), 6.45 (1 H, s), 7.41 (5 H, m); MS m/z (rel intensity) 376 (5, M^+), 374 (5, M^+), 92 (8), 91 (100); IR ($CHCl_3$) ν 1659, 1630, 1595, 1391, 1335 cm^{-1}. An analytical sample was obtained as white crystals, mp 139–140 °C, after recrystallization from ethyl acetate. Anal. Calcd for $C_{18}H_{15}O_4Br$: C, 57.61; H, 4.04. Found: C, 57.78; H, 3.84.

7-(Benzyloxy)-6-bromo-5-methoxy-2-methyl-4*H*-1-benzopyran-4-one (15). To a solution of 7-(benzyloxy)-6-bromo-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (**13**; 50 mg, 0.14 mmol) in iodomethane (5 mL) was added 0.5 g of silver(I) oxide, and the reaction mixture was heated at reflux using a steam bath for 10 min. After cooling, the solid was filtered off and washed with CH_2Cl_2 (10 mL) to give a pale-purple mixture of filtrate and wash. The mixture was evaporated to give a pale-purple solid residue. The residue was separated by preparative TLC (1000-μm plate, 2:1 ethyl acetate/petroleum ether) to give **15** (50 mg, 0.13 mmol, 96%) as a white solid: ^1H NMR ($CDCl_3$) δ 2.29 (3 H, d, J = 0.8 Hz), 3.95 (3 H, s), 5.23 (2 H, s), 6.04 (1 H, q, J = 0.8 Hz), 6.73 (1 H, s), 7.45 (5 H, m); MS m/z (rel intensity) 376 (31, M^+), 374 (31, M^+), 203 (20), 91 (100); IR ($CHCl_3$) ν 1659, 1595, 1391, 1342 cm^{-1}. An analytical sample was obtained as white crystals, mp 162–163 °C, after recrystallization from ethyl acetate. Anal. Calcd for $C_{18}H_{15}O_4Br$: C, 57.61; H, 4.04. Found: C, 57.63; H, 4.21.

7-(Benzyloxy)-8-iodo-5-methoxy-2-methyl-4*H*-1-benzopyran-4-one (16). To a stirred solution of 7-hydroxy-8-iodo-5-methoxy-2-methyl-4*H*-1-benzopyran-4-one[10] (213 mg, 0.641 mmol) in 3:1 (v:v) acetone/DMF (12 mL) was added freshly roasted[14] (over a Meker burner) potassium carbonate (392 mg, 2.83 mmol) followed by benzyl bromide (0.17 mL, 1.4 mmol). The reaction mixture was stirred at room temperature for 16 h under a nitrogen atmosphere. The white solid was filtered off and washed with acetone. The combined filtrate and wash were concentrated in vacuo on a rotary evaporator, and then higher boiling contaminants were removed on a Kugelrohr distillation apparatus (~70 °C/1 Torr) to give a pale-yellow residue. The residue was purified by flash column chromatography on a 1-in. × 10-in. column, eluting with 10:1 $CHCl_3$/methanol, to give **16** (113 mg, 0.268 mmol,

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42%) as a white solid. An analytical sample was obtained as white crystals, mp 143–144 °C, after recrystallization from a mixture of 5:1 ethyl acetate/$CHCl_3$: ^1H NMR ($CDCl_3$) δ 2.37 (3 H, d, J = 0.9 Hz), 3.91 (3 H, s), 5.29 (2 H, s), 6.05 (1 H, q, J = 0.9 Hz), 6.42 (1 H, s), 7.42 (5 H, m); MS m/z (rel intensity) 422 (5, M^+), 331 (2), 303 (3), 176 (3), 91 (100); IR ($CHCl_3$) ν 1652, 1602, 1588, 1335 cm^{-1}. Anal. Calcd for $C_{18}H_{15}O_4I$: C, 51.20; H, 3.59. Found: C, 51.31; H, 3.41.

7-(Benzyloxy)-5-methoxy-8-[4-[3-(methoxycarbonyl)-pyridyl]]-2-methyl-4*H*-1-benzopyran-4-one (17). a. From 10 and 14. A mixture of 7-(benzyloxy)-8-bromo-5-methoxy-2-methyl-4*H*-1-benzopyran-4-one (14; 50 mg, 0.13 mmol), methyl 4-(trimethylstannyl)-3-pyridinecarboxylate (10; 45 mg, 0.15 mmol), and bis(triphenylphosphine)palladium(II) chloride (5 mg, 0.07 mmol; Aldrich) in anhydrous dioxane (2 mL) was heated at 110–115 °C for 3 days under nitrogen with stirring in a sealed tube. The solvent was evaporated, and the residue was separated by preparative TLC (1000-μm plate, 20:1 CH_2Cl_2/MeOH) to give 17 (10 mg, 0.023 mmol, 18%) as a white solid. Recrystallization from ethyl acetate gave white crystals: mp 173–174 °C; ^1H NMR ($CDCl_3$) δ 2.06 (3 H, d, J = 0.9 Hz), 3.65 (3 H, s), 3.97 (3 H, s), 5.15 (2 H, s), 5.98 (1 H, q, J = 0.9 Hz), 6.50 (1 H, s), 7.22 (1 H, d, J = 5.8 Hz), 7.30 (5 H, m), 8.76 (1 H, d, J = 5.8 Hz), 9.20 (1 H, s); MS m/z (rel intensity) 431 (10, M^+) 91 (100). Anal. Calcd for $C_{25}H_{21}NO_6$: C, 69.59; H, 4.92; N, 3.25. Found: C, 69.25; H, 4.68; N, 3.16.

b. From 10 and 16. A mixture of 7-(benzyloxy)-8-iodo-5-methoxy-2-methyl-4*H*-1-benzopyran-4-one (16; 42 mg, 0.10 mmol), methyl 4-(trimethylstannyl)-3-pyridinecarboxylate (10; 41 mg, 0.14 mmol), and bis(triphenylphosphine)palladium(II) chloride (10 mg, 0.014 mmol; Aldrich) in anhydrous toluene (2 mL) was heated at 110–115 °C for 2 days under nitrogen with stirring in a sealed tube. The solvent was evaporated, and the residue was separated by preparative TLC (1000-μm plate, 5:1 ethyl acetate/petroleum ether) to give 17 (9 mg, 0.02 mmol, 20%), identical to the material obtained in part a.

5-(Acetyloxy)-7-(benzyloxy)-6-bromo-2-methyl-4*H*-1-benzopyran-4-one (18). To a well-stirred mixture of 7-(benzyloxy)-6-bromo-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (13; 759 mg, 2.10 mmol), tetrabutylammonium hydrogen sulfate (85 mg, 0.25 mmol), and powdered sodium hydroxide (217 mg, 5.42 mmol) in anhydrous dioxane (75 mL) was added a solution of acetyl chloride (0.75 mL, 10 mmol) in dioxane (15 mL) dropwise over 20 min at room temperature. As soon as addition was complete, the white solid was filtered off and washed with dioxane. The filtrate and wash were concentrated, giving a white solid which was purified by flash column chromatography on a 2-in. × 15-in. column, eluting with 1:1 ethyl acetate/petroleum ether, to give 18 (806 mg, 2.00 mmol, 95%) as a white solid: ^1H NMR ($CDCl_3$) δ 2.30 (3 H, s), 2.48 (3 H, s), 5.22 (2 H, s), 5.98 (1 H, s), 6.82 (1 H, s), 7.44 (5 H, m); MS m/z (rel intensity), 362 (17), 360 (16), 281 (24), 91 (100); IR (Nujol) ν 1764, 1659, 1609, 1349 cm^{-1}. An analytical sample was obtained as white needles, mp 187–188 °C, after recrystallization from acetone. Anal. Calcd for $C_{19}H_{15}O_5Br$: C, 56.59; H, 3.76. Found: C, 56.50, H, 3.65.

7-(Benzyloxy)-5-hydroxy-8-[4-[3-(methoxycarbonyl)-pyridyl]]-2-methyl-4*H*-1-benzopyran-4-one (19). A mixture of 7-(benzyloxy)-8-bromo-5-hydroxy-2-methyl-4*H*-1-benzopyran-4-one (12; 108 mg, 0.299 mmol), methyl 4-(trimethylstannyl)-3-pyridinecarboxylate (10; 178 mg, 0.593 mmol), and bis(triphenylphosphine)palladium(II) chloride (Aldrich; 30 mg, 0.043 mmol) in anhydrous toluene (9 mL) was heated at 110–115 °C for 21 h under argon with stirring in a sealed tube. The solvent was evaporated, and the residue was purified by preparative TLC (three 1000-μm plates, 5:1 ethyl acetate/petroleum ether) to give ~50% recovered 12 and 19 (16 mg, 0.038 mmol, ~25% based on unrecovered 12[15]): ^1H NMR ($CDCl_3$) δ 2.16 (3 H, d, J = 0.7 Hz), 3.65 (3 H, s), 5.09 (2 H, s), 6.03 (1 H, q, J = 0.7 Hz), 6.51 (1 H, s), 7.30 (5 H, m), 7.33 (1 H, d, J = 4.8 Hz), 8.76 (1 H, d, J = 4.8 Hz), 9.20 (1 H, s), 13.02 (1 H, s); MS m/z (rel intensity) 417 (67, M^+), 358 (54), 91 (100); IR ($CHCl_3$) ν 1729, 1659, 1616, 1595, 1391, 1370 cm^{-1}. An analytical sample was obtained as pale-yellow needles, mp 171–172 °C, after recrystallization from ethyl acetate. Anal. Calcd for $C_{24}H_{19}NO_6$: C, 69.05; H, 4.60; N, 3.36. Found: C, 68.71; H, 4.67; N, 3.15.

5-Hydroxy-2-methyl-4*H*,8*H*-pyrano[2′,3′:5,6][1]benzopyrano[3,4-*c*]pyridine-4,8-dione (Schumanniophytine, 1). A stirred mixture of 7-(benzyloxy)-5-hydroxy-8-[4-[3-(methoxycarbonyl)pyridyl]]-2-methyl-4*H*-1-benzopyran-4-one (19; 27 mg, 0.065 mmol) and 10% palladium on activated carbon (54 mg) in 7 mL of anhydrous ethyl acetate was stirred under an atmosphere (balloon pressure) of hydrogen at room temperature for 3 h. The reaction mixture was freed from catalyst by filtration, and the solvent was evaporated. The residue was diluted with $CHCl_3$ (3 mL). The mixture was heated at 55 °C over 16 h. The solvent was evaporated, and the residue was separated by preparative TLC (1000-μm plate, 10:1 $CHCl_3$/MeOH) to give 5-hydroxy-2-methyl-4*H*,8*H*-pyrano[2′,3′:5,6][1]benzopyrano[3,4-*c*]pyridine-4,8-dione (1, schumanniophytine; 11 mg, 0.037 mmol, 58%). A sample was obained as pale-yellow crystals, mp 293–296 °C dec (lit.[1] mp 284–286 °C), after recrystallization from $CHCl_3$: ^1H NMR ($CDCl_3$) δ 2.65 (3 H, d, J = 0.9 Hz), 6.34 (1 H, q, J = 0.9 Hz), 6.81 (1 H, s), 8.48 (1 H, dd, J = 5.7, 0.7 Hz), 8.97 (1 H, d, J = 5.7 Hz), 9.58 (1 H, d, J = 0.7 Hz) 13.47 (1 H, s); MS m/z (rel intensity) 295 (100, M^+), 267 (9), 255 (16); exact mass calcd for $C_{16}H_9NO_5$ $[M]^+$ 295.0481, found 295.0462. The ^1H NMR and low-resolution mass spectral data are in agreement with data reported[1-3] for natural schumanniophytine. Synthetic and natural 1 were also identical by TLC using co-spotting and a variety of solvent systems. The mp of the acetate of synthetic 1 (245–249 °C) is also in agreement with the lit.[1] mp (243–245 °C) of schumanniophytine acetate.

5-(Acetyloxy)-7-(benzyloxy)-6-[4-[3-(methoxycarbonyl)-pyridyl]]-2-methyl-4*H*-1-benzopyran-4-one (20). A mixture of 5-(acetyloxy)-7-(benzyloxy)-6-bromo-2-methyl-4*H*-1-benzopyran-4-one (18; 0.669 g, 1.66 mmol), methyl 4-(trimethylstannyl)-3-pyridinecarboxylate (10; 0.501 g, 1.67 mmol), and bis(triphenylphosphine)palladium(II) chloride (59 mg, 0.084 mmol; Aldrich) in anhydrous dioxane (20 mL) was heated at 110–115 °C for 4 days under nitrogen with stirring in a sealed tube. The solvent was evaporated, and the residue was purified by flash column chromatography on a 1-in. × 16-in. column, eluting with 5:1 ethyl acetate/petroleum ether, to give recovered 18 (~75%) and 20 (67 mg, 36% based on unrecovered 18[15]) as a pale-yellow solid: ^1H NMR ($CDCl_3$) δ 2.14 (3 H, s), 2.32 (3 H, d, J = 0.6 Hz), 3.71 (3 H, s), 5.10 (2 H, s), 6.00 (1 H, q, J = 0.6 Hz), 6.85 (1 H, s), 7.16 (1 H, d, J = 5.1 Hz), 7.30 (5 H, m), 8.75 (1 H, d, J = 5.1 Hz), 9.23 (1 H, s); MS m/z (rel intensity) 459 (1, M^+), 417 (27), 358 (52), 91 (100); IR ($CHCl_3$) ν 1764, 1729, 1659, 1616, 1391, 1342 cm^{-1}. An analytical sample was obtained as white crystals, mp 179–180 °C, after recrystallization from ethyl acetate. Anal. Calcd for $C_{26}H_{21}NO_7$: C, 67.96; H, 4.62; N, 3.05. Found: C, 68.13; H, 4.74; N, 2.95.

12-(Acetyloxy)-9-methyl-5*H*,11*H*-pyrano[3′,2′:6,7][1]-benzopyrano[3,4-*c*]pyridine-5,11-dione (21). A mixture of 5-(acetyloxy)-7-(benzyloxy)-6-[4-[3-(methoxycarbonyl)pyridyl]-2-methyl-4*H*-1-benzopyran-4-one (20; 5.0 mg, 0.011 mmol) and 10% palladium on activated carbon (6 mg) in anhydrous ethyl acetate (2 mL) was stirred under an atmosphere of hydrogen (balloon pressure) at room temperature over 8 h. The reaction mixture was freed from catalyst by filtration (washing with $CHCl_3$), and the solvent was evaporated. The residue was diluted with 2 mL of $CHCl_3$. The mixture was heated at 55 °C for 16 h. The solvent was evaporated to give 21 (2.4 mg, 0.0071 mmol, 65%) as a white solid which was ordinarily used without further purification. A sample was obtained as cream-colored crystals, mp 254–257 °C dec, after recrystallization from a 2:1 mixture of ethyl acetate/$CHCl_3$: ^1H NMR ($CDCl_3$) δ 2.40 (3 H, d, J = 0.6 Hz), 2.66 (3 H, s), 6.09 (1 H, apparent d, J = 0.6 Hz), 7.33 (1 H, s), 8.43[16] (1 H, dd, J = 5.7, 0.9 Hz), 9.00 (1 H, d, J = 5.7 Hz), 9.62 (1 H, d, J = 0.9 Hz); MS m/z (rel intensity) 295 (100, M^+ – ketene); IR ($CHCl_3$) ν 1757, 1659, 1616, 1595, 1356 cm^{-1}.

12-Hydroxy-9-methyl-5*H*,11*H*-pyrano[3′,2′:6,7][1]benzopyrano[3,4-*c*]pyridine-5,11-dione (Isoschumanniophytine, 2). A suspension of 12-(acetyloxy)-9-methyl-5*H*,11*H*-pyrano-

(15) Use of a larger mole fraction of catalyst, longer reaction times, and/or $(Ph_3P)_4Pd$ in place of $(Ph_3P)_2PdCl_2$ led to lower yields.

(16) Reference 2 reports this peak as appearing at δ 8.38, but the spectrum provided (see Acknowledgement) by Professor Houghton shows it at δ 8.44.

[3',2':6,7][1]benzopyrano[3,4-c]pyridine-5,11-dione (21; 3.9 mg, 0.011 mmol) in 1 mL of a saturated solution of HCl in methanol was gently heated on a steam bath for 1 h. The reaction mixture was diluted with water (1 mL), neutralized with saturated aqueous sodium bicarbonate, and then extracted with ethyl acetate (5 mL × 3). The extract was dried ($MgSO_4$) and evaporated, and the residue was separated by preparative TLC (1000-μm plate, 10:1 $CHCl_3$/acetic acid) to give 12-hydroxy-9-methyl-5*H*,11*H*-pyrano[3',2':6,7][1]benzopyran[3,4-c]pyridine-5,11-dione (2, isoschumanniophytine) (1.4 mg, 0.0047 mmol, 43%) as a pale yellow solid which was obtained as pale-yellow crystals, mp 305–308 °C dec, after recrystallization from $CHCl_3$: ^1H NMR ($CDCl_3$) δ 2.46 (3 H, d, J = 0.6 Hz), 6.21 (1 H, q, J = 0.6 Hz), 6.88 (1 H, s), 8.89 (1 H, d, J = 5.7 Hz), 8.96 (1 H, d, J = 5.7 Hz), 9.55 (1 H, s), 15.03 (1 H, s); MS m/z (rel intensity) 295 (M^+, 100), 267 (12); exact mass calcd for $C_{16}H_{10}NO_5$ $[M + H]^+$ 296.0559, found 296.0556. The ^1H NMR and low-resolution mass spectra are in agreement with those recorded[2,3,17] for natural isoschumanniophytine. Synthetic and natural 2 were also identical by TLC using co-spotting and a variety of solvent systems.

Acknowledgment. We thank Professor P. J. Houghton for authentic samples of schumanniophytine and isoschumanniophytine, ^1H NMR spectra of them and their acetates, and other helpful information.

Registry No. 1, 69735-24-6; 2, 96889-79-1; 6, 500-22-1; 8, 138459-35-5; 9, 138459-36-6; 10, 138459-37-7; 11, 20052-28-2; 12, 138459-38-8; 13, 138459-39-9; 14, 138459-40-2; 15, 138459-41-3; 16, 138459-42-4; 17, 138459-43-5; 18, 138459-44-6; 19, 138459-45-7; 20, 138459-46-8; 21, 96889-80-4; 24, 1162-81-8; 25, 1013-69-0; 2,4,6-trihydroxyacetophenone, 480-66-0; 7-hydroxy-8-iodo-5-methoxy-2-methyl-4*H*-1-benzopyran-4-one, 83805-64-5.

(17) The resonances at δ 8.89, 8.96, and 15.03 are incorrectly reported in ref 2. The ^1H NMR spectrum we report is in agreement with a copy of the spectrum furnished (see Acknowledgment) by Professor Houghton.

Fluorinated Chirons for Vitamin D_3 Syntheses. A Serendipitous Synthesis of a 9α-Hydroxy Derivative of (7*Z*)-Vitamin D_3

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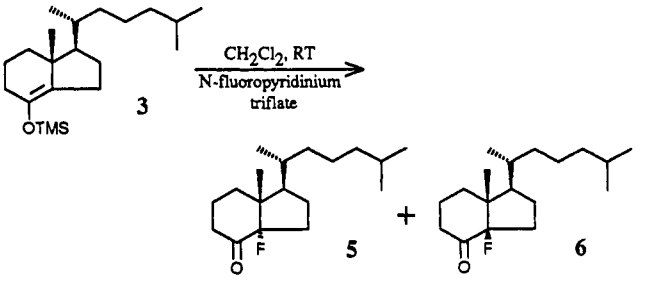
With the discoveries of various biological activities of vitamin D and its metabolites, the development of vitamin D analogues as drugs to be used in the treatment of various diseases has been actively pursued.[1-4] One approach to the discovery of useful vitamin D analogues is to develop analogues that bind strongly to the receptors involved in calcium homeostasis but do not elicit a calcium biological response, thus blocking the vitamin D receptor site from analogues which do elicit a calcium biological response. This is the case of 6-fluorovitamin D_3 (6-F-D_3),[5] which does not display any biological activity in either intestinal calcium absorption (ICA) (Chart I) or bone mobilization (BCM) assays. However, it is the first vitamin D_3 analogue found that binds to the 1,25-$(OH)_2D_3$ receptor in vitro and antagonizes 1,25-$(OH)_2D_3$ activity in vivo.[6] It was assumed that the binding affinity shown by 6-F-D_3 for the receptor is the effect of the fluorine on the triene system of vitamin D_3. The synthesis of 9-fluoro and 14-fluorovitamin D_3 was initiated in order to observe which effects placing fluorine in other positions around the triene system would have on the binding of such compounds to the various vitamin D receptors.

In the synthetic scheme, a suitably fluorinated C/D-ring piece would be coupled to an A-ring piece at the 7,8-bond using a Wittig-type condensation. This path was chosen because the A-ring and C/D-ring carbon skeletons are readily available.[7] Furthermore, the 1α- and 25-hydroxyl groups could easily be incorporated into the synthesis, if desired. The fluorine would be incorporated into the C/D-ring by allowing N-fluoropyridinium triflate[8] to react with the appropriate C/D-ring silyl enol ether (Scheme I).

Treatment of Grundmann's ketone (1)[7] with LDA at −20 °C gave the kinetic enolate which was quenched with trimethylsilyl chloride to give the kinetic silyl enol ether 2 in 82% yield. Conversion of Grundmann's ketone to the thermodynamic silyl enol ether 3 was accomplished by heating the ketone, triethylamine, and trimethylsilyl chloride in DMF at 130 °C for 93 h (73%).

Treatment of the kinetic silyl enol ether 2 with *N*-fluoropyridinium triflate[8] in refluxing methylene chloride for 2 h gave the desired 9α-fluoro C/D-ring ketone 4 in 27% yield (Scheme II). However, the reaction also yielded the 14α-fluoro C/D-ring ketone 5 (9%), the 14β-fluoro C/D-ring ketone 6 (14%), *cis*-Grundmann's ketone (7, 7%), and the α,β-unsaturated ketone 8 (7%). The stereochemistry of the above-described compounds was assigned on the basis of ^1H NMR data.

Treatment of the thermodynamic silyl enol ether 3 with *N*-fluoropyridinium triflate[8] gave the 14α-fluoro C/D-ring ketone 5 in 16% yield and the 14β-fluoro C/D-ring ketone 6 in 27% yield. Again, *cis*-Grundmann's ketone (7) and the α,β-unsaturated ketone 8 were byproducts. It should be noted that the large amount of 14β-fluoro product 6 was quite unexpected. No 9β-fluoro product could be detected in the product mixture when the kinetic silyl enol ether 2 was fluorinated.



Lythgoe and co-workers have shown with model compounds and a total synthesis of vitamin D_3 that coupling of an A-ring phosphine oxide with Grundmann's ketone (1) gives the 7,8-double bond in the proper trans orientation without any cis byproduct.[9] Accordingly, the A-ring phosphine oxide 9[7] was condensed with the C/D-ring ke-

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