Synthesis and Structures of Regioisomeric Hydnocarpin-Type Flavonolignans

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Flavonolignans represent natural compounds whose biosynthesis presumes a radical coupling of a ring B catecholic flavonoid with a molecule of coniferyl alcohol or an analogue. Many natural flavonolignans can exist as regioisomers, depending on how the coupled coniferyl alcohol moiety orients to the flavonoid. These regioisomers are often difficult to separate and have virtually identical NMR spectra. Structural assignments for some have changed with time or have been given without proof. We here report syntheses of both regioisomers of the flavonolignan hydnocarpin and one isomer of a plant isolate previously known as 5′-methoxyhydnocarpin. This isomer, here renamed 5′-methoxyhydnocarpin-D, was recently shown to be a potent inhibitor of a *Staphylococcus aureus* multidrug resistant efflux pump.

In 1968, what was described as the first flavonolignan (silybin) was reported as an isolate from fruits of the medicinal plant *Silybum marianum* and identified on the basis of spectroscopic analysis as either **1a** or **2a**.[1a] It was stated that the data did not distinguish between these structures and that structure **1a** was used only "for convenience" when the data were discussed. It was later shown[1b−d] that silybin was actually **1b** and that another isolate, the regioisomer isosilybin, was **2b**. The second flavonolignan reported, identified in 1973 as an isolate from *Hydnocarpus wightiana*, was given the name hydnocarpin and on the basis of spectroscopy and chemical reactions was assigned structure **3**, "based on analogy with silymarin and also on reactivity considerations".[2] Silymarin was an alternate name for silybin.[3] The spectral data reported for hydnocarpin could not distinguish between **3** and the alternate structure **4,** and there was no discussion of what the "reactivity considerations" were for the assignment. In 1974 the same research group reported on the isolation of two minor components from *H. wightiana*, isohydnocarpin[4] (a structural, not regiochemical isomer of hydnocarpin) and what was termed 5′-methoxyhydnocarpin (**5**).[5] NMR and mass spectral data for the latter isolate as well as for derivatives were presented, and the structure was given as **5** based on these data and "the similarity in the spectra [of the isolate and that of hydnocarpin]". Hydnocarpin was also reported[6] in 1977 from seeds of *Cassia absus* and compared to the *H. wightiana* isolate by spectral data, mixed melting point, co-TLC, and co-IR. (The hydnocarpins were devoid of optical activity and hence are scalemic isolates. The stereochemistry at C-12/C-13 was trans in all these flavonolignans. Structures **1**−**5** (Chart 1) do not imply absolute configurations.)

Shortly thereafter, americanin-A was isolated from *Phytolacca americana* and, on the basis of spectroscopic evidence, given structure **6**.[7] It was recognized that spectroscopic evidence alone could not distinguish between **6** and its regioisomer, and hence definitive proof for **6** was established by correlation of degradation products of **6** derivatives with the same derivatives available from silybin (**1b**) and isosilybin (**2b**). One of the americanin-A degradation products was used to synthesize a trimethyl ether of isolated hydnocarpin, and their identity resulted[8] in a final proof for the structure of hydnocarpin as **4**.

We recently isolated[9] a compound whose ^{1}H and ^{13}C NMR, mass, and UV spectra were essentially identical with those reported for 5′-methoxyhydnocarpin[5] and that was a potent inhibitor of a *Staphylococcus aureus* multidrug resistance efflux pump.[10] To provide more material for testing and to begin to probe bacterial MDR pump inhibitory structure−activity relationships among flavonolignans, we elected to use a synthetic approach. We could find no literature reports on the synthesis of 5′-methoxyhydnocarpin and only a single report[11] on that of hydnocarpin, via coupling of luteolin and coniferyl alcohol in a cell-free suspension culture from fruit of *S. marianum*.

Results and Discussion

Hydnocarpin and Hydnocarpin-D. The literature suggested that horseradish peroxidase[11]-initiated coupling of the flavone luteolin with the lignan coniferyl alcohol in a biomimetic-type reaction might yield hydnocarpin (regioisomer **4**). On the other hand, the same coupling with Ag_2O[1d,12] or Ag_2CO_3[13] should provide regioisomer **3**, an unknown compound here denoted hydnocarpin-D. These preparations were indeed achieved (Scheme 1), although the resulting regioselectivities were less than expected based upon literature results for somewhat analogous systems.[9,12,13] In our hands, **3** and **4** were not separable by usual HPLC methods, although extensive solvent and column variations were not attempted. This parallels difficulties experienced with similar separations in the silybin/isosilybin case.[1d,14] The **3**/**4** ratios in the crude preparations were, however, easily determinable from the ratios of the two ^{1}H NMR doublets for H-13 (in **3**) and H-12 (in **4**), which appeared at δ 4.97 and 5.05, respectively, in DMSO-d_6. These ratios showed the crudes to be 9:1 **3**/**4** for the Ag_2CO_3-catalyzed reaction and 3:2 **4**/**3** for the HRP reaction. ^{13}C NMR resonances for **3** and **4** were essentially identical (all within 0.2 ppm), with the exception of those for C-12 and C-13. For **3**, C-12 was at δ 78.0 and C-13 at δ 76.0, while for **4** C-13 was at δ 78.5 and C-12 at δ 75.9. Although small, these resonance differences were sometimes distinguishable in a mixture of the two. It is debatable if either the ^{1}H or ^{13}C NMR spectra alone would differentiate the two compounds unless both were available.

5′-Methoxyhydnocarpin-D. Because regiochemical mixtures were obtained in the above oxidative coupling reactions, we elected first to attempt a regiospecific synthesis of 5′-methoxyhydnocarpin. In a series of reactions on

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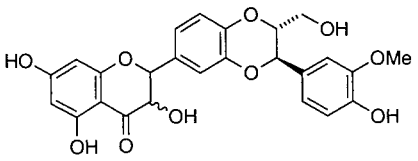
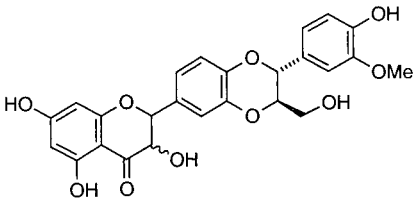
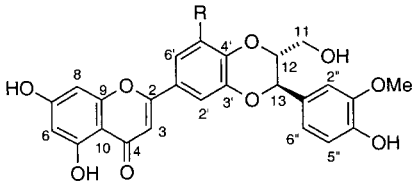
Chart 1



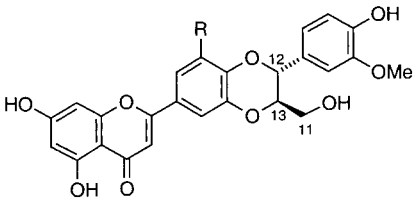
1a: α-OH
1b: β-OH



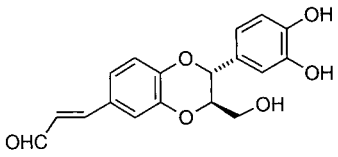
2a: α-OH
2b: β-OH



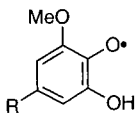
(±)-3: R = H
(±)-5: R = OMe



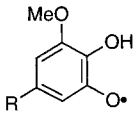
(±)-4: R = H
(±)-9: R = OMe



6



10



11

substituted catechols such as 3,4-dihydroxytoluene and 3,4-dihydroxybenzaldehyde, it was suggested[12] that in the presence of an electron-donating group (such as the methyl on 3,4-dihydroxytoluene) the coupling reaction with coniferyl alcohol would preferentially result in the regioisomer with the pendent aromatic ring down (as in **3**, for example). On the other hand the presence of an electron-withdrawing group (such as the carboxaldehyde on 3,4-dihydroxybenzaldehyde) would result in the opposite regioisomer (as in **4**, for example). We therefore coupled coniferyl alcohol with 3,4-dihydroxy-4-methoxybenzaldehyde (**12**) and then further elaborated the flavonolignan via chalcone **15** (Scheme 2). A single regioisomeric flavonolignan was indeed obtained, but an X-ray diffraction crystal structure of intermediate **7** showed that the final product had to be **5** and not the expected[12] isomer **9**. The NMR spectra were identical with those of the purported 5′-methoxyhydnocarpin.[2,10]

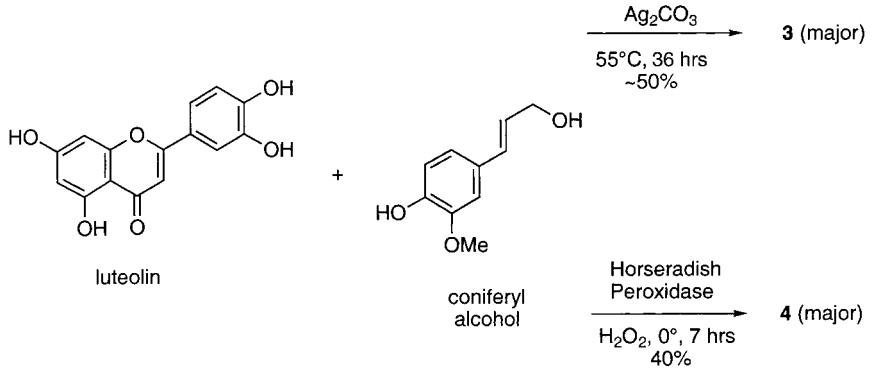
Although the NMR spectra of synthesized **5** and our isolated compound were apparently identical, our experience with **3** and **4** suggested that one could not be certain which was on hand if only one isomer was available. We hence needed independent evidence for the structure of the isolated flavonolignan. This was achieved by HMBC NMR with the coupling constant optimized to 1.6 Hz, a technique similar to the "selective heteronuclear decoupling" experiment used to prove the regiochemistry of coumarinolignoids.[15] As a model, compound **7** (whose structure was known from X-ray) showed the following diagnostic HMBC correlations: H-3 (δ 5.0 resonance) to C-2 (79.1), C-12 (109.7), and C-4a (144.9); H-10 (δ 3.6 resonance) to C-3 (76.2) and C-8a (138.7). The experiment was then repeated on the isolated[9] flavonolignan. Although the same entire array of correlations were not seen, the key H-13 to C-3′ correlation (structure **5**) was indeed seen. Thus, the natural 5′-methoxy compound[2,9,10] does not have the same regiochemistry as hydnocarpin, and hence we have designated it as 5′-methoxyhydnocarpin-D.

Since **3**, **4**, and **5** as well as some additional analogues were found to be inhibitors of the *S. aureus* NorA MDR pump (unpublished results), we desired a sample of true 5′-methoxyhydnocarpin (**9**) for structure−activity relationship studies. By analogy with the syntheses of **3** and **4**, radical-initiated coupling of coniferyl alcohol to the rare flavone selgin might yield a mixture of **5** and **9**. Selgin (**8**), also known as selagine and selagin, was first reported from *Huperzia selago* and its structure proven by spectroscopic analysis and synthesis.[15] We prepared **8** by a much more efficient method (Scheme 3) and then coupled it with coniferyl alcohol using Ag_2CO_3 as well as horseradish peroxidase. Unlike these reactions in the preparation of **3** and **4**, only a single flavonolignan, again **5**, resulted. Regiochemical product ratios from these coupling reactions are probably a result of the relative stability of radicals **10** and/or **11**, where **10** would lead to **5** and **11** would lead to **9.** The methoxy group ortho to the phenoxide radical in **10** may provide extra stabilization which is unavailable in the case of **11**. Where the methoxy group is absent, as in the precursor radicals to **3** and **4**, there is less difference in the radical stabilities and mixtures arising from both radicals are seen.

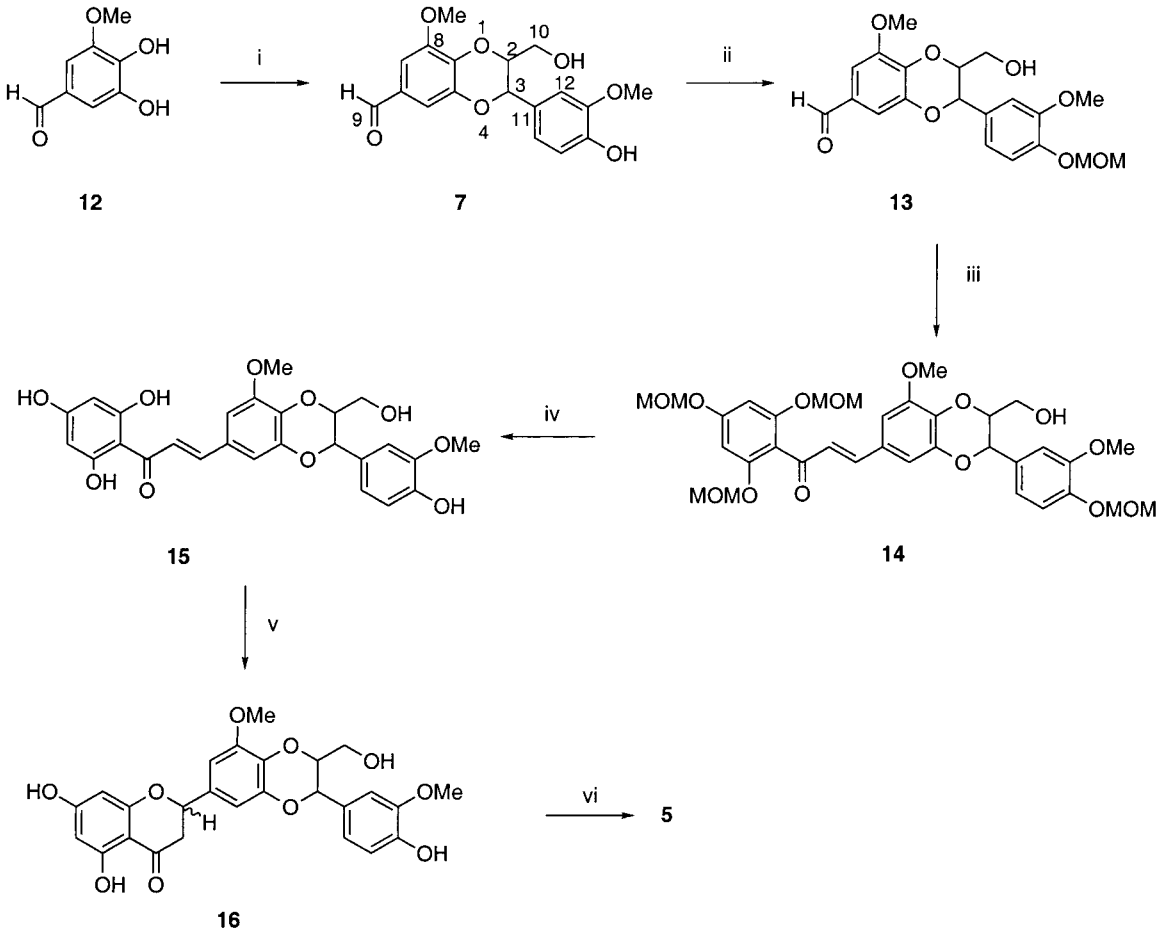
Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$, acetone-*d*,[6] or DMSO-*d*[6] as the solvent and internal reference. Melting points were determined on a Laboratory Device's Mel-Temp and are uncorrected. All solvents were distilled prior to use. THF and 1,4-dioxane were freshly distilled from benzophenone-ketyl and benzene was freshly distilled from CaH_2. ACS acetone was stored over 4 Å molecular sieves. All nonaqueous reactions

Scheme 1. Biomimetic Radical Coupling Syntheses of Hydnocarpin (**4**) and Hydnocarpin-D (**3**)



Scheme 2. Synthesis of 5′-Methoxyhydnocarpin-D (**5**) via an Intermediate (**7**) of Known (X-ray Diffraction) Regiochemistry

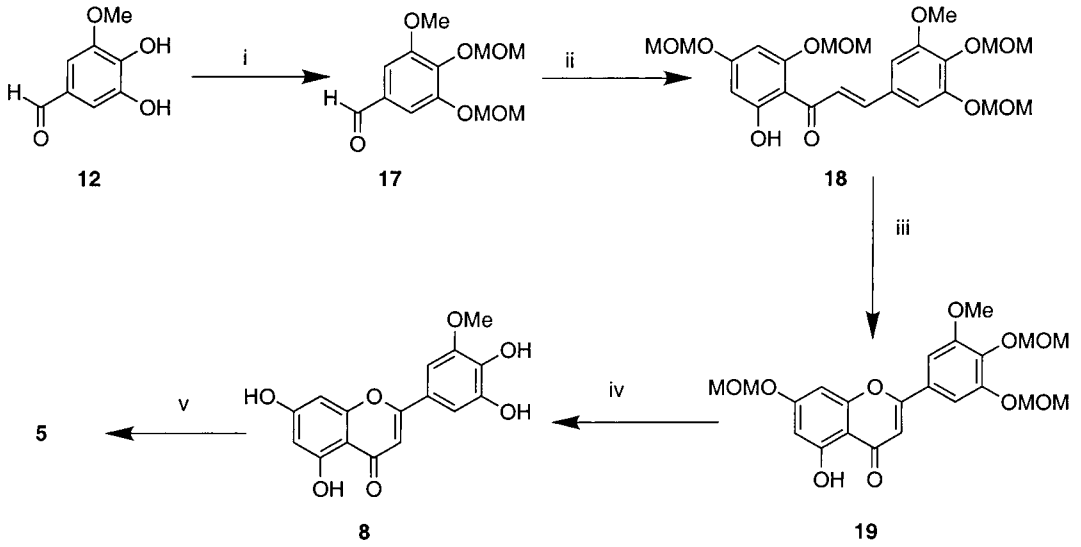


i: coniferyl alcohol, Ag_2CO_3, 5/1 PhH/acetone, 60 °C, 7 h, 72%; **ii**: MOMCl, THF, NaH, rt,7 h, 85%, **iii**: KOH, EtOH, 2,4,6-tris(methoxymethoxy)acetophenone, 48 h, 68%; **iv**: conc. HCl, MeOH, rt, 12 h, 72%; **v**: NaOAc, MeOH, reflux, 3 h, 92%; **vi**: DDQ, dry dioxane, reflux, 36 h, 74%

were performed in dry glassware under an argon atmosphere. All starting materials were used as received. Luteolin was purchased from Indofine Chemical Co., and all other reagents were purchased from Aldrich Chemical Co.

Hydnocarpin-D (3). To a 250 mL three-neck round-bottom flask was added 0.360 g (1.26 mmol) of luteolin and 0.227 g (1.26 mmol) of coniferyl alcohol with 50 mL of dry benzene and 25 mL of dry acetone. The reaction vessel was placed in a 60 °C oil bath and let stir for 10 min. Next, 0.347 g (1.26 mmol) of Ag_2CO_3 was added and the reaction solution stirred vigorously for 36 h. The reaction was then allowed to cool and filtered through a Buchner funnel, and the solvent was removed by rotary evaporation to yield a yellow powder. The yellow powder was subjected to column chromatography (CC) using 95:5 $CHCl_3$/MeOH to yield 0.220 g of a 9:1 (by NMR) mixture of **3** and **4** plus other minor impurities. The sample was recrystallized from 9:1 MeOH/H_2O to yield 0.125 g (21%) of pure **3** and **4**. This mixture was acetylated using standard acetic anhydride/pyridine conditions to yield an off-white powder, which was washed with acetone until bright white. A standard deprotection using K_2CO_3/MeOH was used to remove the acetyl groups and yielded 0.040 g (7%, yellow-white powder) of pure **3**: ^{1}H NMR (DMSO-d_6) δ 3.37 (dd, J = 12.6, 4.8 Hz, H-11a), 3.57 (dd, J = 12.6, 2.8 Hz, H-11b), 4.31 (m, H-12), 4.97 (d, J = 8.0 Hz, H-13), 6.19 (*d*, J = 2.0 Hz, H-6), 6.51 (d, J = 2.0 Hz, H-8), 6.82 (dd, J = 8.0, 1.6 Hz, H-5″), 6.87 (s, H-3), 6.89 (dd, J = 8.0, 1.6 Hz, H-6″), 7.05 (d, J = 1.6 Hz, H-2″), 7.12 (d, J = 8.4 Hz, H-5′), 7.63 (dd, J = 8.8, 2.0 Hz,

Scheme 3. Biomimetic Synthesis of 5′-Methoxyhydnocarpin-D (**5**) via the Flavone Selgin (**8**)



i: MOMCl, K_2CO_3, dry acetone, 0.25 h, 85%; **ii**: KOH, EtOH, 2-hydroxy-4,6-bis(methoxymethoxy)acetophenone, 17 h; 75%; **iii**: DDQ, dry dioxane, reflux, 48 h, 65%; **iv**: HCl, MeOH, reflux, 20 min., 72%; **v**: coniferyl alcohol, Ag_2CO_3, 5/1 PhH/acetone, 60 °C, 7 h, 33%.

H-6′), 7.67 (d, J = 2.0 Hz, H-2′), 9.18 (br s), 10.85 (br s), 12.90 (br s); ^{13}C NMR (DMSO-d_6) δ 55.7 (OMe), 60.0 (C-11), 75.9 (C-13), 78.5 (C-12), 94.1 (C-8), 98.9 (C-6), 103.8 (C-3), 103.8 (C-10), 111.8 (C-2″), 115.0 (C-2′), 115.3 (C-5″), 117.4 (C-5′), 120.1 (C-6′), 120.6 (C-6″), 123.4 (C-1′), 127.0 (C-1″), 144.0 (C-4′), 146.9 (C-3′), 147.1 (C-4″), 147.6 (C-3″), 157.3 (C-9), 161.4 (C-5), 162.9 (C-7), 164.2 (C-2), 181.8 (C-4). Peracetate: ^{1}H NMR ($CDCl_3$) δ 2.08 (s), 2.34 (s), 2.35 (s), 2.44 (s), 3.88 (s, OMe), 4.03 (dd, J = 12.4, 4.0 Hz), 4.34 (m), 4.41 (dd, J = 12.0, 3.0 Hz), 5.00 (d, J = 8 Hz), 6.57 (s), 6.84 (d, J = 2.1 Hz), 6.98 (d, J = 1.8 Hz), 7.02 (m), 7.11 (*d*, J = 8.7 Hz), 7.12 (d, J = 7.8 Hz), 7.32 (d, J = 2.1), 7.45 (dd, J = 8.4, 2.1), 7.53 (d, J = 2.1); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.1, 21.1, 21.2, 56.0, 62.4, 75.9, 76.3, 107.5, 108.9, 110.9, 113.5, 115.3, 117.8, 119.7, 120.2, 123.3, 124.4, 133.9, 140.6, 143.6, 146.0, 150.0, 151.6, 153.7, 157.4, 161.8, 167.9, 168.6, 169.3, 170.2, 176.2; mp 233−234 °C; *anal.* C 63.00%, H 4.11%, calcd for $C_{33}H_{28}O_{13}$, C 62.66%, H 4.46%.

Hydnocarpin (4). To a 100 mL three-neck round-bottom flask was added 0.300 g (1.05 mmol) of luteolin and 0.189 g (1.05 mmol) of coniferyl alcohol. Next, 20 mL of dry ACS acetone and 5 mL of a 0.2 M citric acid/phosphate buffer were added to the reaction flask, and the flask was cooled to 0 °C. Two drops of 30% H_2O_2 and 1 mL of a horseradish peroxidase solution (1.5 mg HRP (1100 U/mg)/3 mL water) were added. The HRP solution (1 mL) was added every 15 min thereafter, and the reaction then allowed to stir at 0 °C for 7 h. The reaction solution was allowed to warm to room temperature, washed with brine, and extracted with EtOAc. The EtOAc was dried with anhydrous $MgSO_4$, filtered, and removed by rotary evaporation to yield a brown-orange solid. This solid was subjected to CC using 95:5 $CHCl_3$/MeOH to yield 0.187 g (40%) of a white-yellow solid, 3:2 ratio of **4** to **3** by ^{1}H NMR. This solid was further purified by reversed-phase (C-18) vacuum-liquid chromatography (75:25 H_2O/MeOH to 20:80 H_2O/MeOH) to yield 0.087 g of a white-yellow solid that was recrystallized from 9:1 MeOH/H_2O to yield 0.025 g (5%, white-yellow powder, mp 258−259 °C) of pure **4**. ^{1}H and ^{13}C NMR spectra were essentially identical to the literature.[16]

3-(4-Hydroxy-3-methoxyphenyl)-2-hydroxymethyl-8-methoxy-2,3-dihydrobenzo[1,4]dioxine-6-carbaldehyde (7). To a 250 mL three-neck round-bottom flask was added 0.486 g (2.77 mmol) of **12** and 0.500 g (2.77 mmol) of coniferyl alcohol with 100 mL of dry benzene and 20 mL of dry acetone. This solution was allowed to stir 20 min in a 60 °C oil bath, and then 0.765 g (2.77 mmol) of Ag_2CO_3 was added and the reaction stirred vigorously for 7 h. The reaction was then allowed to cool and filtered through a Buchner funnel, and the solvent was removed by rotary evaporation to yield a brown microcrystalline solid. This solid was subjected to CC using 4:6 hexanes/EtOAc to yield 0.687 g (72%) of a near pure sample of **7**. This solid was recrystallized from 7:3 EtOH/H_2O to yield 0.344 g (36%, white microcrystalline solid, mp 103−105 °C) of pure **7**: ^{1}H NMR ($CDCl_3$) δ 3.60 (dd, J = 12.6, 4.0 Hz), 3.93 (s, OMe), 3.94 (m), 3.97 (s, OMe), 4.10 (m), 4.99 (*d*, J = 8.0 Hz), 6.94 (br s, 1H), 6.97 (m, 2 H), 7.13 (d, J = 2.0 Hz), 7.16 (d, J = 2.0 Hz), 9.80 (s); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.3, 61.2, 76.1, 79.1, 103.0, 109.6, 114.6, 114.8, 120.8, 127.3, 129.4, 138.7, 144.4, 146.5, 147.0, 149.5, 190.8; *anal.* C 62.55%, H 5.00%, calcd for $C_{18}H_{16}O_7$, C 62.61%, H 4.96%.

2-Hydroxymethyl-8-methoxy-3-(3-methoxy-4-methoxymethoxyphenyl)-2,3-dihydrobenzo[1,4]dioxine-6-carbaldehyde (13). To a 100 mL round-bottom flask was added 0.196 g (0.569 mmol) of **7** and 35 mL of dry THF. The flask was placed into an ice−water bath, and 0.017 g (0.683 mmol) of NaH (washed prior with hexanes) was added. The solution was stirred 1 h, then 0.055 g (0.683 mmol) of MOMCl was added, and the reaction was allowed to warm to room temperature. The reaction was stirred for 6 h at room temperature, poured into a saturated solution of $NaHCO_3$, and extracted with EtOAc. The EtOAc was dried with anhydrous $MgSO_4$, filtered, and removed by rotary evaporation to yield an off-white microcrystalline solid. This solid was subjected to CC using 3:7 hexanes/EtOAc to yield 0.187 g (85%, white microcrystalline solid, mp 67−68 °C) of pure **13**: ^{1}H NMR ($CDCl_3$) δ 3.52 (s), 3.60 (dd, J = 12.0, 3.3 Hz), 3.91 (s, OMe), 3.93 (m), 3.95 (s, OMe), 4.10 (m), 5.03 (d, J = 8.1 Hz), 5.25 (s), 6.98 (d, J = 1.8 Hz), 6.99 (dd, J = 8.7, 1.8 Hz), 7.12 (d, J = 1.8 Hz), 7.15 (d, J = 1.8 Hz), 7.20 (d, J = 8.7 Hz), 9.79 (s); ^{13}C NMR ($CDCl_3$) δ 30.9, 56.0, 56.2, 61.2, 75.9, 78.9, 95.3, 103.0, 110.5, 114.5, 116.2, 120.0, 129.3, 129.5, 138.6, 144.2, 147.1, 149.4, 149.9, 190.6.

3-[2-Hydroxymethyl-8-methoxy-3-(3-methoxy-4-methoxymethoxyphenyl)-2,3-dihydrobenzo[1,4]dioxin-6-yl]-1-(2,4,6-trismethoxymethoxyphenyl)propenone (14). To a 25 mL round-bottom flask was added 0.098 g (0.252 mmol) of **13** and 0.076 g (0.252 mmol) of 2,4,6-tris(methoxymethoxy)-acetophenone, 10 mL of EtOH, and 0.339 g of crushed solid KOH. The blocked acetophenone was prepared from reaction of the bis-protected acetophenone[18] with NaH (1.3 equiv) and MOMCl (1.3 equiv) in THF at 0 °C for 4 h (86%). This was stirred at room temperature for 17 h, washed with brine, and extracted with EtOAc. The EtOAc was dried with anhydrous $MgSO_4$, filtered, and removed by rotary evaporation to yield a yellow oil, which was subjected to CC 2:8 using hexanes/EtOAc

to yield 0.115 g (68%, yellow solid) of pure **14**: ^{1}H NMR (acetone-d_6) δ 3.36 (s), 3.46 (s), 3.52 (dd, J = 12.8, 3.6 Hz), 3.83 (m), 3.85 (s, OMe), 3.89 (s, OMe), 4.14 (m), 5.06 (d, J = 7.6 Hz), 5.14 (s), 5.19 (s), 5.22 (s), 6.88 (d, J = 2.0 Hz), 6.88 (d, J = 16.0 Hz), 6.98 (d, J = 2.0 Hz), 7.03 (dd, J = 8.4, 2.0 Hz), 7.15 (d, J = 8.4 Hz), 7.17 (d, J = 2.0 Hz), 7.24 (d, J = 16.0 Hz); ^{13}C NMR (acetone-d_6) δ 56.3, 56.3, 56.3, 56.4, 56.4, 56.5, 61.6, 76.8, 79.6, 95.3, 95.3, 95.4, 95.4, 96.3, 97.9, 105.2, 111.4, 112.7, 118.1, 121.1, 128.1, 128.6, 132.2, 136.8, 145.5, 148.0, 150.5, 151.5, 156.6, 160.3, 193.6.

3-[2-Hydroxymethyl-8-methoxy-3-(4-hydroxy-3-methoxyphenyl)-2,3-dihydrobenzo[1,4]dioxin-6-yl]-1-(2,4,6-trihydroxyphenyl)propenone (15). To a 25 mL round-bottom flask was added 0.042 g of **14**, 5 mL of MeOH, and 2 drops of concentrated HCl. This solution was stirred at room temperature for 17 h, poured into a saturated $NaHCO_3$ solution, and extracted with EtOAc. The EtOAc was dried with anhydrous $MgSO_4$, filtered, and removed by rotary evaporation to yield a brown-orange oil that was subjected to CC using 92:8 $CHCl_3$/MeOH to yield 0.022 g (72%, brown-orange microcrystalline solid, mp 175−177 °C) of pure **15**: ^{1}H NMR (acetone-d_6) δ 3.52 (dd, J = 12.8, 3.6 Hz), 3.83 (m), 3.88 (s, OMe), 3.91 (s, OMe), 4.13 (m), 5.03 (d, J = 8.0 Hz), 5.97 (s), 6.89 (d, J = 8.0 Hz), 6.93 (d, J = 2.0 Hz), 6.94 (d, J = 2.0 Hz), 6.98 (dd, J = 8.0, 2.0 Hz), 7.14 (d, J = 2.0 Hz), 7.70 (d, J = 15.6 Hz), 8.13 (d, J = 15.6 Hz); ^{13}C NMR (acetone-d_6) δ 56.4, 56.5, 61.8, 77.1, 79.8, 96.2, 105.8, 106.1, 110.8, 112.0, 115.9, 121.7, 126.7, 128.8, 129.2, 136.9, 143.4, 145.8, 148.2, 148.6, 150.4, 165.6, 165.8, 193.2; *anal*. C 56.10%, H 5.42%, calcd for $C_{26}H_{24}O_{10}\cdot 3.5H_2O$, C 55.81%, H 5.58%.

5,7-Dihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-hydroxymethyl-8-methoxy-2,3-dihydrobenzo[1,4]dioxin-6-yl]chroman-4-one (16). To a 50 mL round-bottom flask was added 0.021 g (0.043 mmol) of **15**, 15 mL of MeOH, and 0.035 g (0.43 mmol) of NaOAc. This solution was heated at reflux for 3 h, poured into a saturated $NaHCO_3$ solution, and extracted with EtOAc. The EtOAc was dried with anhydrous $MgSO_4$, filtered, and removed by rotary evaporation to yield an off-white solid. This solid was subjected to CC using 1:9 hexanes/EtOAc to afford 0.019 g (90%, white powder) of **16** as a 1:1 (^{1}H NMR) diastereomeric mixture (from integration of the singlets at δ 12.170 and δ 12.173): ^{1}H NMR ($CDCl_3$) δ 3.19 (d, J = 12.4 Hz), 3.23 (d, J = 12.8 Hz), 3.52 (m), 3.81 (m), 3.87 (s, OMe), 3.88 (s, OMe), 4.07 (m), 5.01 (d, J = 7.6 Hz), 5.45 (dd, J = 12.4, 2.4 Hz), 5.89 (m), 5.95 (m), 6.76 (m), 6.83 (m), 6.88 (d, J = 8.0 Hz), 6.98 (dd, J = 8.0, 2.0 Hz), 7.13 (m), 7.76 (bs), 9.62 (bs), 12.17 (bs); HRFAB$^+$ 497.1430 (calcd for $C_{26}H_{25}O_{10}$ 497.1447).

5′-Methoxyhydocarpin-D (5). To a 25 mL round-bottom flask was added 0.016 g (0.032 mmol) of **16**, 0.018 g of DDQ (0.081 mmol), and 7 mL of dry 1,4-dioxane. The solution was heated at reflux for 36 h and allowed to cool, and the solvent was removed by rotary evaporation to yield a dark brown solid. The solid was chromatographed on 95:5 $CHCl_3$/MeOH to yield 0.012 g of pure **5** (72%, pale yellow powder): HRFAB$^+$ m/z 495.1310 (calcd for $C_{26}H_{23}O_{10}$ 495.1291); ^{1}H and ^{13}C NMR spectral data were identical with those of the isolate.[9]

1-(2-Hydroxy-4,6-bis-methoxymethoxyphenyl)-3-(3-methoxy-4,5-bis-methoxymethoxyphenyl)propenone (18). To a 100 mL three-neck round-bottom flask was added 0.202 g (1.20 mmol) of **12**, 1.75 g (16.22 mmol) of K_2CO_3 and 35 mL of dry acetone. This solution was stirred for 10 min, then 0.242 g (3.00 mmol) of MOMCl was added. The solution was heated at reflux for 15 min, poured into a saturated $NaHCO_3$ solution, and extracted with EtOAc. The EtOAc was dried with anhydrous $MgSO_4$, filtered, and removed by rotary evaporation to yield a brown, viscous oil. The oil was subjected to CC using 1:1 hexanes/EtOAc to yield a near pure sample of **17** (0.262 g, 85%, clear oil that partially solidified upon standing), which was carried directly to the next step. To a 50 mL round-bottom flask was added 0.129 g (0.505 mmol) of **17**, 0.129 g (0.505 mmol) of 2-hydroxy-4,6-bis(methoxymethoxy)acetophenone,[18] 20 mL of EtOH, and 0.680 g (12.12 mmol) of crushed solid KOH. This was stirred at room temperature for 17 h, brought to pH 7 using 1 N HCl, and extracted with EtOAc. The EtOAc was dried with anhydrous Mg_2SO_4, filtered, and removed by rotary evaporation to yield a bright yellow oil. The oil was subjected to CC using 1:1 hexanes/EtOAc to yield 0.154 g (75%, yellow solid) of pure **18**: ^{1}H NMR ($CDCl_3$) δ 3.49 (s), 3.52 (s), 3.54 (s), 3.63 (s), 3.90 (s, OMe), 5.19 (s), 5.20 (s), 5.25 (s), 5.30 (s), 6.26 (d, J = 2.4 Hz), 6.33 (d, J = 2.4 Hz), 6.86 (d, J = 2.0 Hz), 7.17 (d, J = 2.0 Hz), 7.71 (d, J = 15.6 Hz), 7.87 (d, J = 15.6 Hz); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.2, 56.5, 56.9, 57.2, 94.0, 94.6, 95.0, 95.3, 97.5, 98.4, 106.9, 107.4, 108.6, 127.0, 131.6, 137.3, 142.4, 151.4, 153.5, 159.9, 163.5, 167.4, 192.6; *anal*. C 58.11%, H 6.16%, calcd for $C_{24}H_{30}O_{11}$, C 58.29%, H 6.12%.

5-Hydroxy-2-(3-methoxy-4,5-bis-methoxymethoxyphenyl)-7-methoxymethoxychromen-4-one (19). To a 25 mL round-bottom flask was added 0.095 g (0.192 mmol) of **18**, 0.109 g (0.480 mmol) of DDQ, and 10 mL of dry 1,4-dioxane. This solution was heated at reflux for 48 h and allowed to cool, and solvent was removed by rotary evaporation to yield a dark brown solid. This solid was subjected to CC using 97:3 CH_2Cl_2/Me_2CO to yield 0.056 g (65%, pale yellow powder, mp 122−123 °C) of pure **19**: ^{1}H NMR ($CDCl_3$) δ 3.52 (s), 3.55 (s), 3.63 (s), 3.97 (s, OMe), 5.23 (s), 5.27 (s), 5.29 (s), 6.50 (d, J = 2.4 Hz), 6.63 (s), 6.69 (d, J = 2.4 Hz), 7.14 (d, J = 2.4 Hz), 7.34 (d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 56.3, 56.4, 56.4, 57.3, 94.1, 94.3, 95.4, 98.4, 100.2, 104.4, 105.8, 106.3, 107.8, 127.0, 138.8, 151.4, 153.8, 157.6, 162.0, 163.0, 163.8, 182.4; *anal*. C 58.83%, H 5.27%, calcd for $C_{22}H_{24}O_{10}$ C 58.93%, H 5.39%.

Selgin (8). To a 25 mL round-bottom flask was added 0.092 g (0.291 mmol) of **19**, 3 mL of 3 N HCl, and 10 mL of MeOH. This solution was heated at reflux for 20 min, allowed to cool, washed with a saturated $NaHCO_3$ solution, and extracted with EtOAc. The EtOAc was dried with anhydrous $MgSO_4$, filtered, and removed by rotary evaporation to yield 0.047 g (72%, pale yellow powder) of pure **8**. The ^{1}H NMR spectrum was essentially the same as in the literature,[15] but the ^{13}C NMR spectrum was not previously reported: ^{1}H NMR (DMSO-d_6) δ 3.87 (s, OMe), 6.20 (d, J = 2.0 Hz), 6.48 (d, J = 2.0 Hz), 6.83 (s), 7.15 (d, J = 2.0 Hz), 7.17 (d, J = 2.0 Hz), 9.25 (bs), 9.41 (bs), 10.85 (bs), 12.98 (bs); ^{13}C NMR (DMSO-d_6) δ 56.3, 93.2, 98.8, 102.4, 103.3, 103.7, 107.5, 120.4, 138.6, 146.0, 148.6, 157.3, 161.5, 163.9, 164.2, 181.8.

5′-Methoxyhydnocarpin-D (5). To a 50 mL three-neck round-bottom flask was added 0.011 g (0.035 mmol) of **8**, 0.007 g (0.035 mmol) of coniferyl alcohol, 15 mL of dry benzene, and 7.5 mL of dry acetone. The flask was placed in a 60 °C oil bath and stirred for 20 min. Next, 0.010 g of Ag_2CO_3 was added and the reaction solution stirred vigorously for 7 h. The reaction was then allowed to cool and filtered through a Buchner funnel, and the solvent was removed by rotary evaporation to yield a yellow powder. The powder was subjected to CC using 8:2 CH_2Cl_2/Me_2CO to yield 0.006 g (33%, pale yellow powder) of pure **1**. ^{1}H and ^{13}C spectral data were identical with those of **5** prepared regiospecifically (see above) and with those of the isolate.[9]

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Supporting Information Available: X-ray diffraction data for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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