Acid-Catalyzed Cyclization of 2,3-Dibenzylidenesuccinates: Synthesis of Lignans (±)-Cagayanin and (±)-Galbulin

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Acid-catalyzed cyclizations of *E,E*-dibenzylidenesuccinate esters have been developed as an efficient synthetic route to 1-aryl-1,2-dihydronaphthalenes. This reaction has been used in the synthesis of the naturally occurring lignans (±)-cagayanin and (±)-galbulin.

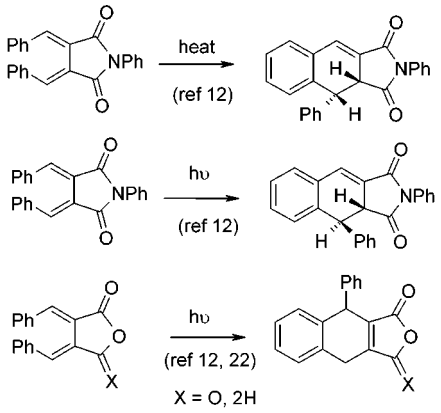
Introduction

The 1,2-dihydronaphthalene carbon skeleton is found in many lignans, a class of natural products found in plants. Although many methods have been devised to prepare such lignans,[1−10] only a few have made use of *E,E*-dibenzylidenesuccinate derivatives as starting materials for such syntheses. Among the exceptions are the photochemical and thermal cyclizations of fulgides and fulgimides, the cyclic anhydrides and imides of *E,E*-dibenzylidenesuccinic acids[11−20] (Scheme 1). Reports have also been made of the photochemical cyclization of the corresponding lactones[21,22] (Scheme 1).

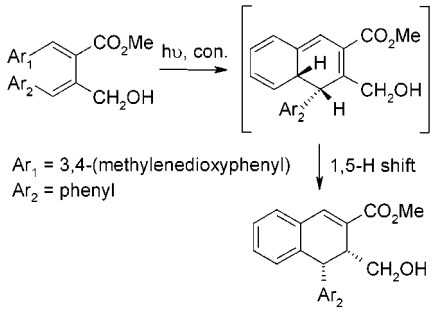
There appears to be only one example of the photocyclization reaction of an acyclic derivative of an *E,E*-dibenzylidenesuccinate[22] (Scheme 2).

The ease with which *E,E*-dibenzylidenesuccinates can be prepared by the Stobbe condensation makes them attractive starting materials for lignan synthesis, and so, we embarked on a program to explore more general methods of achieving the cyclization of *E,E*-dibenzylidenesuccinates to dihydronaphthalenes.

Scheme 1. Cyclization of Fulgides and Fulgimides



Scheme 2. Cyclization of an Acyclic *E,E*-Dibenzylidenesuccinate Derivative



Because simple diesters of *E,E*-dibenzylidenesuccinate are very easily prepared, we began our investigation with a study of these esters. Judging from previous observations for the photochemical cyclization shown in Scheme 2, it was expected that the photocyclization of *E,E*-dibenzylidenesuccinate diesters would give conrotatory ring closure. A subsequent suprafacial 1,5-sigmatropic shift of hydrogen (in accordance with the pericyclic reaction rules) would afford dihydronaphthalenes with a cis relationship between the substituents on positions 1 and 2 (as in Scheme 2). On the other hand, an acid-

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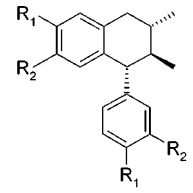


Cagayanin (**1**); $R_1,R_2 = OCH_2O$
Galbulin (**2**); $R_1 = R_2 = OMe$

Figure 1. Cagayanin and galbulin.

catalyzed cyclization would likely provide dihydronaphthalenes with the thermodynamically more stable trans relationship between these two substituents.

Both of these predictions have been realized, and the methodolgy has been exploited to prepare the naturally occurring lignans (±)-cagayanin, and (±)-galbulin (Figure 1).

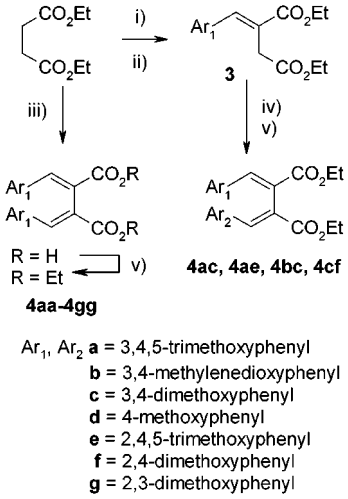
Cagayanin (**1**) was first isolated from the nutmeg of *Myristica cagayanesis* Merr, and the extract has been used medicinally in China.[23] Until now, no synthetic approach has been reported for this compound. Galbulin (**2**) was first isolated from *Himantandra baccata* Bail in 1954.[24] A number of papers[25−35] have reported the synthesis of galbulin (**2**), many starting from other known lignans of similar structure. Most recently, R. J. Whitby et al. described an interesting stereoselective synthesis of (±)-galbulin using a metal-mediated cyclization of a 1,7 diene.[35]

Results and Discussion

Symmetrical 2,3-dibenzylidenesuccinate diethyl esters were prepared by a one-pot, double Stobbe condensation reaction of diethyl succinate with 2 equiv of an aromatic aldehyde followed by esterification with ethyl iodide in acetone/DMSO (Scheme 3). Unsymmetrical 2,3-dibenzylidenesuccinate diethyl esters were prepared by a two-step Stobbe condensation reaction using two different aldehydes (Scheme 3).

We began our investigation of the cyclization of the *E,E*-dibenzylidenesuccinate diesters by studying the photochemistry of diethyl *E,E*-bis-(3,4,5-trimethoxybenzylidene)succinate (**4aa**). Irradiation of **4aa** in ethanol with 0.01 M TFA for 2 h followed by chromatographic separation, yielded the *cis*- (34%) and *trans*- (2%) 1,2-dihydronaphthylene diethyl esters **5ap** and **6ap**, respectively (Scheme 4). An acidic solvent was used, as it was found that this suppressed the formation of some minor side products.

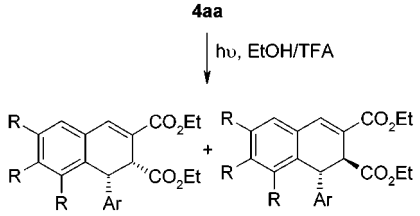
Scheme 3. Synthesis of Diethyl *E,E*-Dibenzylidenesuccinates[a]



Ar_1, Ar_2 **a** = 3,4,5-trimethoxyphenyl
b = 3,4-methylenedioxyphenyl
c = 3,4-dimethoxyphenyl
d = 4-methoxyphenyl
e = 2,4,5-trimethoxyphenyl
f = 2,4-dimethoxyphenyl
g = 2,3-dimethoxyphenyl

[a] (i) Ar_1−CHO, KO*t*-Bu, *t*-BuOH; (ii) EtI, K_2CO_3, acetone; (iii) 2 Ar_1−CHO, NaH, DMF; (iv) Ar_2−CHO, NaOEt, EtOH; (v) EtI, K_2CO_3, acetone/DMSO.

Scheme 4. Photocyclization of an *E,E*-Dibenzylidenesuccinate Diester



Ar = 3,4,5-trimethoxyphenyl, R = OMe

This result encouraged us to study the photochemistry of other dibenzylidenesuccinate diethyl esters, such as *E,E*-bis-(2,4,5-trimethoxybenzylidene)succinate diethyl ester **4dd**. Irradiation of **4dd** under the same conditions as used for **4aa** gave only recovery of starting material. Employing longer irradiation times, changing the solvent to ethyl acetate, and using a basic or neutral solvent (K_2CO_3 in ethanol or pure ethanol) failed to produce any significant amounts of cyclized product. In some instances, the starting material was slowly consumed to produce a complex mixture of products. The NMR spectrum of the crude product mixture from these latter reactions exhibited peaks that could be interpreted to indicate *E,Z*-isomerization of the starting material (although these isomers were not isolated or characterized). Irradiation of diesters **4bb** and **4cc** also did not produce significant amounts of the cyclized products. As a result of these unpromising results, we began an investigation of the acid-catalyzed cyclization of the *E,E*-dibenzylidenesuccinate diethyl esters.

After some experimentation, it was discovered that diethyl ester **4aa** would undergo cyclization in the presence of trifluoromethanesulfonic acid (triflic acid) to give the expected *trans*-1,2-dihydronaphthalene **6ap**, along with some dearylyzed product **7p**. The generality

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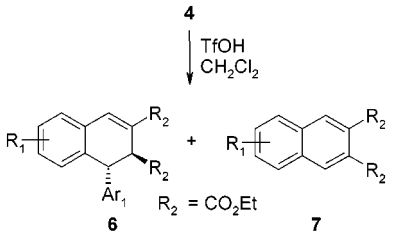
Scheme 5. Acid-Catalyzed Cyclization of Diethyl *E,E*-Dibenzylidenesuccinates



Ar_1, Ar_2 **a** = 3,4,5-trimethoxyphenyl
b = 3,4-methylenedioxyphenyl
c = 3,4-dimethoxyphenyl
d = 4-methoxyphenyl
e = 2,4,5-trimethoxyphenyl
f = 2,4-dimethoxyphenyl
g = 2,3-dimethoxyphenyl

R_1 **p** = 6,7,8-trimethoxy
q = 6,7-methylenedioxy
r = 6,7-dimethoxy
s = 7-methoxy
t = 5,7,8-trimethoxy
u = 5,7-dimethoxy
v = 5,6-dimethoxy

Table 1. Acid-Catalyzed Cyclization of 2,3-Dibenzylidenesuccinate Diethyl Esters.

entry	diester	acid (equiv)	time (h)	products (yields, %)[a]
1	**4aa**	1.5	8	**6ap** (63), **7p** (17)[b]
2	**4bb**	1.5	18	**6bq** (36), **7q** (~5)[b,c]
3	**4cc**	1.0	3	**6cr** (59), **7r** (17)
4	**4dd**	1.5	22	**6ds** (55)
5	**4ee**	0.1	4	**6et** (97)
6	**4ff**	0.1	22	**6fu** (38)[c]
7	**4gg**	0.1	120	**6gv** (~10)[d]
8	**4gg**	1.5	17	**6gv** (85)
9	**4bc**	1.5	3	**6br** + **6cq** (68), **7q** (11)
10	**4ac**	1.0	18	**6ar** (24), **6cp** (16), **7p** (43)[c]
11	**4ae**	0.1	46	**7p** (97)
12	**4cf**	0.1	21	**7r** (95)

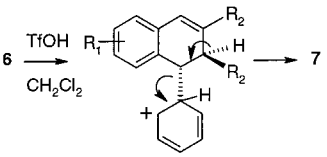
[a] Isolated yields. [b] Starting material (25%) was recovered. [c] Reaction was carried out at room temperature. [d] Yield was estimated from ^{1}H NMR spectrum of the crude reaction mixture.

of the reaction was demonstrated by application to a variety of dibenzylidenesuccinate diethyl esters (Scheme 5).

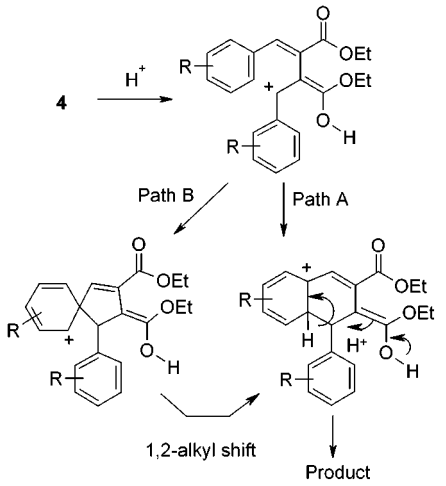
The results are summarized in Table 1.

The results from Table 1 show that the reactivity of the diesters highly depends on the position of the alkoxy substituents on the aryl rings. For instance, cyclization of diesters **4aa** and **4bb** was sluggish and did not go to completion. Prolonged heating or the use of excess triflic acid decreased the yields of the desired products while making the dearylized compounds (**7p** and **7r**) the major products. Moderate yields were obtained using 1.5 equiv of triflic acid. Diester **4cc** cyclized more readily and gave **6cr** in 59% yield. **4ee** and **4ff**, bearing 3′-methoxy groups, cyclized rapidly in the presence of catalytic amounts (10 mol %) of triflic acid. Diester **4gg** required 1.5 equiv of triflic acid and 17 h to yield 85% of **6gv**. Unsymmetrical dibenzyledenesuccinate diester **4bc** gave 68% of an inseparable mixture (3:1 ratio) of what appeared to be two regeoisomers, along with 11% of dearylized product (**7q**). The major ring cyclization appears to have occurred on the 3,4-dimethoxyphenyl ring, as determined by a comparison of the NMR spectrum of the mixture of cyclized products to the spectrum of dihydronaphthalene

Scheme 6. Mechanism of Acid-Catalyzed Dearylation



Scheme 7. Mechanism of Acid-Catalyzed Cyclization



6cb prepared by an alternate route.[7] Similarly, diester **4ac** gave the two regeoisomers **6ar** (24%) and **6cp** (16%), along with dearylized product **7p** (43%). Unsymmetrical 3,4-dibenzyledenesuccinate diesters, in which one of the aromatic rings bears a 3′-methoxy group (**4ae** and **4cf**), appear to selectively cyclize on the other aryl ring (the ring without the 3′-methoxy substituent), but in these cases, no dihydronaphthalenes were isolated, as they were quantitatively converted to the dearylized products (97 and 95%, respectively) under the reaction conditions. The driving force for the dearylization most likely arises from the aromatization of the dihydronaphthalene to the more stable naphthalene derivatives.

Dearylation most likely involves acid-catalyzed elimination of the aryl group from the dihydronaphthalene products by a two-step mechanism with protonation of the ipso carbon as the first step. Similar dearylation mechanisms have been proposed previously.[36] A possible mechanism is shown in Scheme 6.

Judging from the effects of substituents on the ease of cyclization, as well as previous mechanistic investigations of the cyclization of aryl butyl systems,[37] it seems likely that the catalyzed cyclization of dibenzylidenesuccinates follows, at least in part, path B, as shown in Scheme 7.

Syntheses of (±)-Cagayanin (1) and (±)-Galbulin (2)

Syntheses of (±)-cagayanin and (±)-galbulin were completed following the procedure shown in Scheme 8.

The dihydronaphthalenes diesters **6bq** and **6cr** were prepared using the method described above in 36 and 59% yields, respectively (Table 1). Palladium-catalyzed hydrogenation of the 1,2-dihydronaphthalenes **6bq** and

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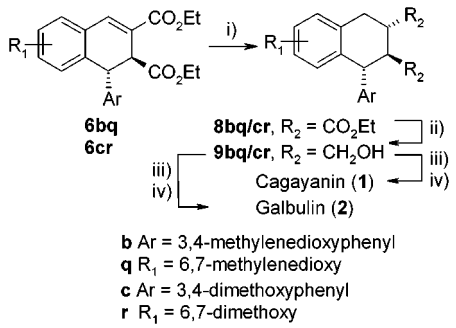
Scheme 8. Synthesis of Cagayanin and Galbulin[a]



[a] (i) H_2, Pd, EtOH; (ii) LAH, THF, rt; (iii) Tf_2O, CH_2Cl_2, Et_3N, −10 °C; (iv) LAH, THF, −10 °C.

6cr gave aryltetralin derivatives **8bq** and **8cr** in 64 and 92% yields, respectively. Reduction of **8bq** and **8cr** with lithium aluminum hydride in THF gave the diols **9bq** and **9cr**, respectively, in nearly quantitative yields. These products were immediately used for the next reaction without purification. The crude diols were converted to their corresponding ditriflates using triflic anhydride in CH_2Cl_2 at −10 °C and then reduced using lithium aluminum hydride in THF. This provided the natural products (±)-cagayanin (**1**) (77%) and (±)-galbulin (**2**) (43%). Syntheses of (±)-cagayanin and (±)-galbulin were completed in overall 18% (from **3bb**) and 23% (from **3cc**) yields, respectively. The present method should be applicable to the syntheses of other lignans and related compounds.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 FT instrument using residual $CHCl_3$ in $CDCl_3$ as the internal standard unless otherwise specified. Silicycle silica gel was used for all chromatography. HRMS/mass spectra were obtained on a VG Analytical 7070E-HF instrument.

General Procedure A for the Preparation of Symmetrical Diethyl 2,3-Dibenzylidenesuccinates (4bb, 4dd−4gg). A three-neck round-bottom flask (100 mL) fitted with reflux condenser and dropping funnel was charged with 1.260 g of NaH (52.5 mmol, 57% in mineral oil) and dry DMF (10 mL). A mixture of aldehyde (25 mmol) and diethylsuccinate (10 mmol) in 50 mL of dry DMF was slowly added to the stirred suspension via the dropping funnel. After addition was complete, the mixture was heated to reflux (100 °C bath temperature) and stirred under a nitrogen atmosphere overnight. The mixture was cooled to room temperature, aqueous KOH solution (0.1 M, 30 mL) was added, the solution was refluxed for 1.5 h. The solution was then cooled to room temperature, water (60 mL) was added, and the solution was extracted with EtOAc, with these extracts being discarded. The aqueous layer was acidified with 10% HCl (pH 1) and extracted again with EtOAc. The combined EtOAc extracts were washed with water and brine, dried over magnesium sulfate, and evaporated to give the crude product. The crude product was dissolved in acetone/DMSO (3:1, 50 mL), ethyl iodide (7.28 mL, 93 mmol) and solid K_2CO_3 (12.9 g, 93 mmol) were added, and the mixture was refluxed under nitrogen atmosphere overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure, water (100 mL) was added, and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over magnesium sulfate, and evaporated. Column chromatography (ethyl acetate/hexanes) yielded the pure products in 50−60% yield (based on diethyl succinate).

Synthesis of Diethyl *E*-(3,4,5-Trimethoxybenzylidene)-succinate (3a) and *E*-(3,4-Dimethoxybenzylidene)succinate (3c). Diethyl esters **3a** and **3c** were prepared according to a literature procedure[9,10] in 67 and 85% yields, respectively. These compounds had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[9,10]

General Procedure B for the Preparation of Unsymmetrical Diethyl *E,E*-Dibenzylidenesuccinates. Sodium ethoxide (3.0 mmol) was prepared by dissolving sodium (0.069 g, 3.0 mmol) in absolute ethanol (5 mL) in a 100-mL three-neck round-bottom flask. A mixture of diester **3a** or **3c** (2.0 mmol) and an appropriate aldehyde (2.5 mmol) in absolute ethanol (20 mL) was slowly added (ca. 15 min) through a dropping funnel. The solution was then refluxed under nitrogen atmosphere for 3−5 h. The mixture was cooled to room temperature and evaporated under reduced pressure, distilled water (50 mL) was dded, and the mixture was extracted with ethyl acetate. The organic layers were discarded, and the aqueous layer was acidified with 10% aqueous HCl (pH 1) and extracted with EtOAc. The combined organic fractions were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give the crude product. This crude product was dissolved in acetone/DMSO (4:1, 25 mL), solid K_2CO_3 (1.39 g, 10.0 mmol) and ethyl iodide (0.78 mL, 10 mmol) were added, and the mixture was refluxed under nitrogen for 6−15 h. The reaction mixture was cooled to room temperature, the acetone was evaporated, distilled water (60 mL) was added, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried with magnesium sulfate, and concentrated to give the desired 2,3-dibenzylidenesuccinate diethyl esters in 81−97% isolated yields (symmetrical diesters **4aa** and **4cc** were also prepared using this procedure).

Diethyl *E,E*-Bis-(3,4,5-trimethoxybenzylidene)succinate (4aa). 4aa was prepared from **3a** and 3,4,5-trimethoxybenzaldehyde using general procedure B. The crude product was purified by column chromatography using 35−45% EtOAc in hexanes to give a light yellow oil, which solidified on standing (87% from **3a**), mp 144.0−145.0 °C (from hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 6H, J = 7.1 Hz), 3.74 (s, 12H), 3.80 (s, 6H), 4.14 (m, 4H), 6.75 (s, 4H), 7.80 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1 (2C), 56.0 (4C), 60.9 (2C), 61.1 (2C), 107.1 (4C), 126.8 (2C), 130.2 (2C), 139.4 (2C), 142.1 (2C), 153.0 (4C), 166.8 (2C); mass spectrum *m*/*z* (relative intensity) 530 (M^+, 6), 317 (17), 289 (13), 181 (100); HRMS calcd for $C_{28}H_{34}O_{10}$ 530.2151, found 530.2146.

Photoreaction of Diethyl *E,E*-Bis-(3,4,5-trimethoxybenzylidene)succinate (4aa). A solution of the diethyl ester **4aa** (0.202 g, 0.381 mmol) in a 0.01 M solution of TFA in anhydrous ethanol (60 mL) in a Pyrex test tube was purged vigorously with N_2 for 5 min (the nitrogen atmosphere was maintained for the duration of the reaction), the test tube was sealed, and the mixture was irradiated for 3 h using a medium-pressure Hanovia mercury lamp. The solution was evaporated, and the residue was redissolved in CH_2Cl_2, dried over anhydrous magnesium sulfate, and concentrated under vacuum to afford a pale yellow oil (0.213 g). The product mixture was purified by flash column chromatography on silica gel (100 mL) using 30% EtOAc in hexanes to afford two fractions. The first chromatography fraction (0.004 g, 2%) exhibited a ^{1}H NMR spectrum identical to that of the *trans*-dihydronaphthalene **6ap**.[9]

The second eluted fraction (0.070 g, 34%) was a colorless wax: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.2 Hz), 1.24 (t, 3H, J = 7.2 Hz), 3.46 (s, 3H), 3.71 (s, 3H), 3.72 (s, 6H), 3.82 (s, 3H), 3.86 (s, 3H), 4.08 (dd, 1H, J = 2.8, 9.1 Hz), 4.17 (m, 2H), 4.76 (d, 1H, J = 9.1 Hz), 6.32 (s, 2H), 6.63 (s, 1H), 7.36 (d, 1H, J = 2.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 14.3, 40.5, 48.1, 56.10, 56.13 (2C), 60.4, 60.5, 60.7, 60.8 (2C), 106.4 (2C), 108.0, 123.7, 126.2, 127.1, 135.4, 136.4, 137.2, 144.2, 151.1, 152.6 (2C), 152.9, 167.3, 171.5; mass spectrum *m*/*z* (relative intensity) 530 (M^+, 100), 484 (44), 456 (62), 411 (65), 384 (33), 358 (69); HRMS calcd for $C_{28}H_{34}O_{10}$ 530.2151, found 530.2139.

General Procedure for Acid-Catalyzed Cyclization of Diethyl *E,E*-3,4-Dibenzylidenesuccinates. A two-neck round-bottom flask fitted with a condenser was purged with nitrogen. A solution of diester (0.5 mmol) in freshly distilled CH_2Cl_2 (10 mL) was added to the reaction flask via cannula. The solution was warmed to 45 °C, triflic acid was added (see Table 1), and

the solution was refluxed under nitrogen atmosphere for several hours (see Table 1). The reaction mixture was cooled to room temperature, quenched with 5% aqueous sodium bicarbonate solution (10 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The crude product was purified by silica gel column chromatography using EtOAc in hexanes to produce pure 1,2-dihydronaphthalene derivatives.

The ^{1}H NMR, ^{13}C NMR, and mass spectral properties of *trans*-1,2-dihydro-naphthalene-2,3-dicarboxylate derivatives **6ap**, **6bq**, **6cr**, **6et**, **6br**, **6cr**, **6ar**, and **6cp** were identical to those previously reported.[9,10]

Diethyl 7-Methoxy-*r*-1-(4-methoxyphenyl)-*trans*-1,2-dihydronaphthalene-*t*-2,3-dicarboxylate (6ds). The crude product was purified by column chromatography using 15−20% EtOAc in hexanes to give a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.1 Hz), 1.29 (t, 3H, J = 7.1 Hz), 3.74 (s, 3H), 3.76 (s, 3H), 3.98 (d, 1H, J = 3.4 Hz), 4.07 (m, 2H,), 4.21 (m, 2H), 4.61 (d, 1H, J = 3.4 Hz), 6.64 (d, 1H, J = 2.5 Hz), 6.75 (d, 2H, J = 8.7 Hz), 6.79 (dd, 1H, J = 2.5, 8.3 Hz), 6.97 (d, 2H, J = 8.7 Hz), 7.28 (d, 1H, J = 8.4 Hz), 7.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 46.0, 47.3, 55.17, 55.24, 60.6. 61.0, 112.8, 113.9 (2C), 114.8, 122.8, 124.7, 128.7 (2C), 130.6, 134.4, 137.1, 139.3, 158.4, 161.4, 166.7, 172.5; mass spectrum *m*/*z* (relative intensity) 410 (M^+, 9), 336 (100), 308 (10), 291 (49), 264 (63), 250 (14), 227 (19), 189 (11), 149 (19), 135 (26), 121 (22); HRMS calcd for 410.1729 $C_{24}H_{26}O_6$ found 410.1741.

Diethyl 6,7,8-Trimethoxynaphthalene-2,3-dicarboxylate (7p). The crude product was purified by column chromatography using 30% EtOAc in hexanes to give a colorless oil, which solidified on standing, mp 50.0−52.0 °C (from hexanes/ether). ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, J = 7.1 Hz), 1.39 (t, 3H, J = 7.1 Hz), 3.98 (s, 6H), 4.06 (s, 3H), 4.38 (q, 2H, J = 7.1 Hz), 4.40 (q, 2H, J = 7.1 Hz), 6.99 (s, 1H), 8.04 (s, 1H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2, 56.0 (CH_3), 61.2, 61.4, 61.5, 61.6, 102.8, 124.2, 124.5, 126.6, 128.2, 129.0, 131.0, 142.5, 148,4, 155.2, 167.9, 168.0; mass spectrum *m*/*z* (relative intensity) 362 (M^+, 100), 347 (32), 319 (16), 289 (37), 245 (9), 231 (12), 202 (9); HRMS calcd for $C_{19}H_{22}O_7$ 362.1365 found 362.1347.

Diethyl 6,7-Methylenedioxynaphthalene-2,3-dicarboxylate (7q). The crude product was purified by column chromatography using 35% EtOAc in hexanes to give a colorless viscous oil, which solidified on standing at 4 °C, mp 107.0−109.0 °C (from hexanes/ether). ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 6H, J = 7.1 Hz), 4.39 (q, 4H, J = 7.1 Hz), 6.01(s, 2H), 7.15 (s, 2H), 8.02 (s, 2H);^{13}C NMR ($CDCl_3$) δ 14.2 (2C), 61.5 (2C), 101.7, 104.4 (2C), 127.6 (2C), 128.7 (2C), 131.0 (2C), 149.7 (2C), 167.9 (2C); mass spectrum *m*/*z* (relative intensity) 316 (M^+, 42), 271 (6), 243 (100), 149 (31); HRMS calcd for $C_{17}H_{16}O_6$ 316.0946 found 316.0934.

Diethyl 6,7-Dimethoxynaphthalene-2,3-dicarboxylate (7r). The crude product was purified by column chromatography using 30% EtOAc in hexanes to give a colorless viscous oil, which solidified on standing at 4 °C, mp 123.0−125.0 °C (from hexanes/EtOAc). ^{1}H NMR ($CDCl_3$) δ 1.38 (t, 6H, J = 7.1 Hz), 3.99 (s, 6H), 4.39 (q, 4H, J = 7.1 Hz), 7.15 (s, 2H), 8.07 (s, 2H);^{13}C NMR ($CDCl_3$) δ 14.2 (2C), 56.0 (2C), 61.5 (2C), 106.7 (2C), 127.3 (2C), 128.2 (2C), 129.5 (2C), 151.4 (2C), 168.0 (2C); mass spectrum *m*/*z* (relative intensity) 332 (M^+, 43), 287 (17), 259 (100), 214 (17), 186 (22), 115 (9); HRMS calcd for $C_{18}H_{20}O_6$ 332.1259 found 332.1261.

Diethyl *r*-1-(3,4-Methylenedioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene-*t*-2,*c*-3-dicarboxylate (8bq). Dihydronaphthalene diester (**6bq**) (0.032 g, 0.07 mmol) was dissolved in anhydrous EtOH (15 mL), and Pd/C (0.015 g, 0.1 mmol) was added. The reaction flask was flushed and evacuated with H_2 several times; then the mixture was stirred at room temperature for 27 h under H_2. The reaction mixture was filtered through Celite and concentrated to give a light yellow oil (0.020 g, 64%). The product was used in the next step with no further purification. ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3H, J = 7.1 Hz), 1.25 (t, 3H, J = 7.1 Hz), 2.97 (t, 1H, J = 10.8 Hz), 3.06 (m, 2H), 3.13 (m, 1H), 3.96 (m, 2H), 4.08 (m, 1H, J = 11.0 Hz), 4.14 (m, 2H), 5.85 (m (AB), 2H), 5.92 (s, 2H), 6.22 (s, 1H), 6.54 (d, 1H, J = 1.6 Hz), 6.56 (s, 1H), 6.60 (dd, 1H, J = 1.7, 7.8 Hz), 6.71 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 32.4, 43.4, 49.2, 51.5, 60.4, 60.9, 100.8, 100.9, 107.7, 107.9, 109.0, 109.1, 122.6, 127.2, 131.0, 136.8, 146.2, 146.3, 146.6, 147.9, 173.5, 173.9; mass spectrum *m*/*z* (relative intensity) 440 (M^+, 32), 366 (47), 263 (26), 235 (21), 220 (12), 135 (22); HRMS calcd for $C_{24}H_{24}O_8$ 440.1471 found 440.1473.

Diethyl *r*-1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-*t*-2,*c*-3-dicarboxylate (8cr). Dihydronaphthalene diester (**6cr**) (0.15 g, 0.3 mmol) was stirred with Pd/C (0.023 g, 0.2 mmol) under hydrogen atmosphere for 18 h, as described above, to afford a colorless oil (0.14 g, 92%). The product was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz), 3.00 (t, J = 10.8 Hz), 3.06−3.24 (m, 3H), 3.57 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 3.92 (m, 2H), 4.12 (m, 2H), 4.14 (d, 1H of C1, J = 10.7 Hz), 6.22 (s, 1H), 6.59 (d, 2H, J = 2.2 Hz), 6.68 (dd, 1H, J = 2.1, 8.2 Hz), 6.78 (d, 1H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 31.9, 43.4, 49.0, 51.5, 55.8, 55.9, 60.3, 60.9, 110.7, 110.9, 111.9, 112.1, 121.7, 126.2, 129.9, 135.4, 147.5, 147.7, 148.0, 149.0, 173.7, 174.1; mass spectrum *m*/*z* (relative intensity) 472 (M^+, 50), 398 (42), 325 (100), 269 (22), 236 (20), 151 (29); HRMS calcd for $C_{26}H_{32}O_8$ 472.2097 found 472.2086.

***r*-1-(3,4-Methylenedioxyphenyl)-6,7-methylenedioxy-1,2,3,4-tetrahydronaphthalene-*t*-2,*c*-3-di(hydroxymethyl) (9bq).** Aryltetralin diester **8bq** (0.020 g, 0.05 mmol) was dissolved in THF (3 mL) and added to a slurry of lithium aluminum hydride (LAH) (0.024 g, 0.6 mmol) and dry THF (2 mL) at room temperature. The reaction was stirred under N_2 for 0.5 h at room temperature and then worked up using Fieser's method.[38] In succession, 0.06 mL of water, 0.06 mL of 15% aqueous NaOH, and 0.18 mL of water were added to quench the reaction. The solution was diluted with EtOAc (15 mL), dried with $MgSO_4$, filtered through Celite, and evaporated to give an oil (0.016 g, 100%). ^{1}H NMR ($CDCl_3$) δ 1.71−1.83 (m, 1H), 1.93−2.03 (m, 1H), 2.55 (br s, 2H) 2.68 (m, 2H), 3.48 (dd, 1H, J = 5.2, 11.3 Hz), 3.72 (m, 2H), 3.78 (m, 2H), 5.83 (m (AB), 2H), 5.92 (s, 2H), 6.20 (s, 1H), 6.54 (d, 1H, J = 1.8 Hz), 6.55 (s, 1H), 6.64 (dd, 1H, J = 1.7, 7.8 Hz), 6.74 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 33.6, 39.8, 48.2, 48.3, 62.7, 66.3, 100.6, 100.9, 107.8, 108.0, 109.1, 109.6, 122.8, 129.2, 132.8, 139.1, 145.7, 145.8, 146.2, 148.0; mass spectrum *m*/*z* (relative intensity) 356 (M^+, 100), 338 (32), 307 (73), 280 (54), 267 (50), 238 (52), 210 (27), 185 (26), 173 (50), 152 (41), 135 (89), 115 (29), 76 (19); HRMS calcd for $C_{20}H_{20}O_6$ 356.1259 found 356.1262.

***r*-1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-*t*-2,*c*-3-di(hydroxymethyl) (9cr).** Aryltetralin diester **8cr** (0.14 g, 0.3 mmol) was reduced with LAH (0.066 g, 1.7 mmol) in THF as described above to yield a colorless amorphous solid (0.10 g, 92%). This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those reported previously.[39]

(±)-Cagayanin (1). Aryltetralin diol **9bq** (0.016 g, 0.05 mmol) was taken up in dry CH_2Cl_2 (4 mL), and diisopropylethylamine (0.018 g, 0.1 mmol) added. The flask was purged with N_2 and cooled to −10 °C in a salt/ice water bath. Triflic anhydride (0.039 g, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the cooled reaction mixture. The reaction mixture was stirred under N_2 for 1.5 h, and water (3 mL) was added to quench the reaction. The solution was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 10 mL). The organic fraction was dried with $MgSO_4$, filtered, and evaporated. The crude product was dissolved in THF (2 mL) and added to a slurry of LAH (0.018 g, 0.5 mmol) in THF (2 mL) at −10 °C. The reaction mixture was stirred under N_2 at room temperature for 45 min and worked up by Fieser's

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method (60 μL of water, 60 μL of 15% aqueous NaOH, 180 μL of water), followed by the addition of EtOAc (20 mL). The solution was dried with $MgSO_4$, filtered through Celite, and evaporated to give a colorless oil. This crude product was purified by column chromatography using 20% EtOAc/hexanes to give a clear, colorless oil (0.011 g, 77%). This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those previously reported.[23]

(±)-Galbulin (2). Aryltetralin diol **9cr** (0.027 g, 0.07 mmol) was reacted with triflic anhydride and reduced following a method identical to that described above for **9bq**. The crude product was purified by column chromatography using 30% EtOAc/hexanes to give a light yellow oil (0.011 g, 43%). This compound had ^{1}H NMR, ^{13}C NMR, and mass spectral properties identical to those reported previously.[24]

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Supporting Information Available: Characterization data for **4bb**, **4cc**, **4dd**, **4ff**, **4bc**, **4ac**, **4ae**, **4cf**, **6fu**, and **6gv** and ^{13}C and ^{1}H NMR spectra of **4aa**, **4ac**, **4ae**, **4bb**, **4bc**, **4cc**, **4cf**, **4dd**, **4ee**, **4ff**, **4gg**, **5ap**, **6ds**, **6fu**, **6gv**, **7p**, **7q**, **7r**, **8bq**, **8cr**, **9bq**, **1**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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