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Total Synthesis of (+)-Demethoxycardinalin 3

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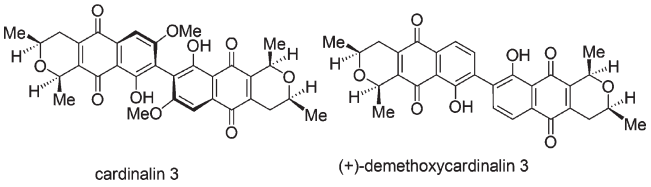

The total synthesis of (+)-demethoxycardinalin 3 is described. The synthetic strategy features the synthesis of dimeric Fischer carbene and its use in a bidirectional Dötz benzannulation reaction to set the dimeric structure of the cardinalins. The oxa-Pictet−Spengler reaction was used to construct the pyran rings. The synthesis is completed in seven steps and an overall yield of 7%.

The pyranonaphthoquinone antibiotics are isolated from various strains of bacteria and fungi and exhibit a wide range of biological activities against a variety of Gram-positive bacteria, pathogenic fungi, and yeasts.[1] They have also been shown to act as alkylating agents upon bioreduction in a mode resembling the antitumor drug mitomycin C.[2] The dimeric pyranonaphthoquinones like the cardinalins,[3] crisamicins,[4] and actinorhodins[5] have also emerged as important cytotoxic compounds. The cardinalins 1−3 (Figure 1) have been isolated from the New Zealand toadstool *Dermocybe cardinalis*.[3] Their structures were determined by spectroscopic methods. Buchanan et al.[3b] have shown that the crude ethanolic extract of *Dermocybe cardinalis* is a potent inhibitor of the growth of P388 murine leukemia cells (IC_{50} 0.47 μg cm^{-3}). They have also pointed out that cardinalin 3 (**3**), like **1** and **2**, showed no evidence of asymmetric doubling in either the ^1H or ^{13}C NMR spectra. Hence, **1**−**3** occur as discrete atropisomers, and from the CD spectra studied **1**−**3** are believed to possess (*S*)-axial chirality. The syntheses of

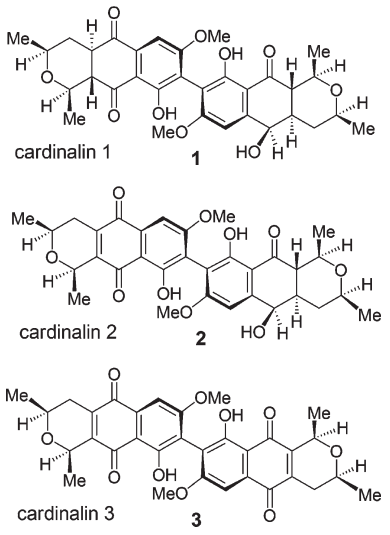

FIGURE 1. Cardinalins 1−3.

monomeric pyranonaphthoquinones are well documented.[6] However, synthetic efforts in the dimeric class of pyranonaphthoquinones are rather scarce. While the synthesis of natural (−)-cardinalin 3 (**3**) is not yet realized, the syntheses of racemic **3**[7] and its core structure[8] are documented. The racemic synthesis by de Koning and co-workers[7] is based on Ullmann coupling to get the racemic biaryl unit and subsequent Stobbe condensation to build the naphthalene structure. The *cis*-pyran rings are derived through the Wacker-type reaction and subsequent hydrogenation. The core structure synthesis by Brimble and co-workers[8] is based on phthalide annulation by the Hauser-Kraus method and the late-stage homocoupling strategy. As part of our ongoing research in the asymmetric synthesis of pyranonaphthoquinones[9] and related compounds employing the Fischer carbenes and the Dötz benzannulation reaction, we became interested in the dimeric structure of the cardinalins. We visualized synthesizing the dimeric Fischer carbenes,[10] and through a bidirectional approach using Dötz benzannulation[11] and oxa-Pictet Spengler[12] reactions, the dimeric pyranonapthoquinone core of cardinalin 3 could be

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(2) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249–280.
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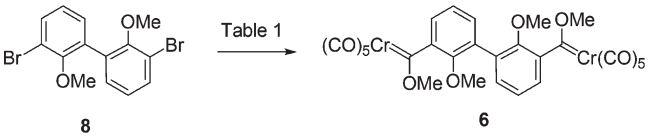
TABLE 1. Optimization of the Synthesis of Dimeric Fischer Carbene 6

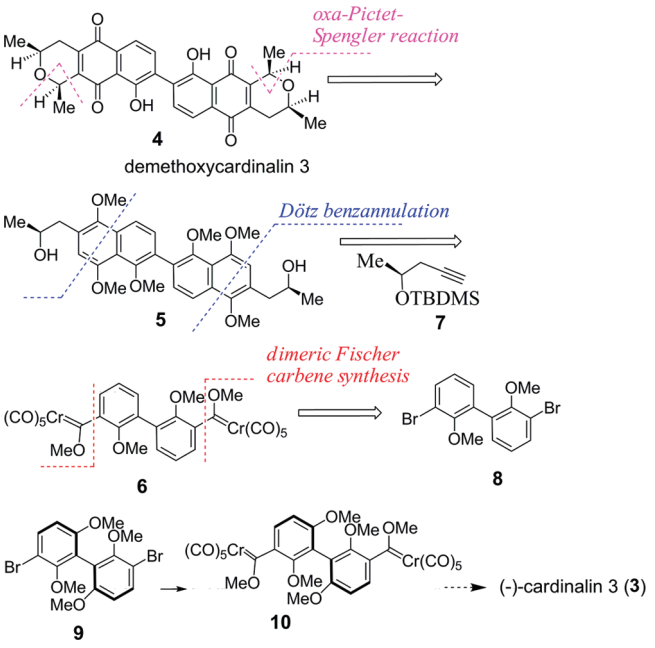


8 6

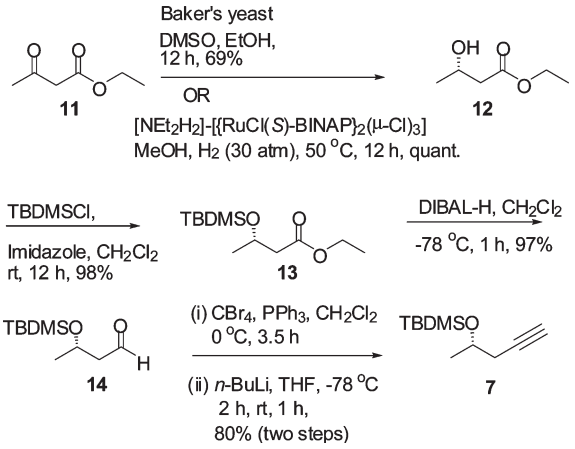
entry	reaction conditions[a]	**6** (%)
1	(i) *n*-BuLi, THF, rt, 2 min; (ii) $Cr(CO)_6$, THF, 0 °C, 1 h, rt, 2 h; (iii) Me_3OBF_4, CH_2Cl_2, 0 °C, 1 h, rt, 2 h	27
2	(i) *n*-BuLi, THF, 0 °C, 5 min; (ii) $Cr(CO)_6$, THF, 0 °C, 1 h, rt, 2 h; (iii) Me_3OBF_4, CH_2Cl_2, 0 °C, 1 h, rt, 2 h	36
3	(i) *n*-BuLi, THF, −78 °C, 5 min; (ii) $Cr(CO)_6$, THF, 0 °C, 1 h, rt, 2 h; (iii) Me_3OBF_4, CH_2Cl_2, 0 °C, 1 h, rt, 2 h	49
4	(i) *n*-BuLi, Et_2O, rt, 15 min; (ii) $Cr(CO)_6$, Et_2O, 0 °C, 1 h, rt, 3 h; (iii) Me_3OBF_4, CH_2Cl_2, 0 °C, 1 h, rt, 3 h	41
5	(i) *n*-BuLi, Et_2O, 0 °C, 30 min; (ii) $Cr(CO)_6$, Et_2O, 0 °C, 1 h, rt, 3 h; (iii) Me_3OBF_4, CH_2Cl_2, 0 °C, 1 h, rt, 3 h	44
6	(i) *n*-BuLi, Et_2O, −78 °C, 30 min; (ii) $Cr(CO)_6$, Et_2O, 0 °C, 1 h, rt, 3 h; (iii) Me_3OBF_4, CH_2Cl_2, 0 °C, 1 h, rt, 3 h	58

[a]The solution of bis-lithiated intermediate of **8** was added to the suspension of $Cr(CO)_6$ in ether or THF, and then the mixture was concentrated after the reaction time specified in the table. The residue was then diluted with CH_2Cl_2 and treated with Me_3OBF_4.

SCHEME 1. Retrosynthetic Analysis of Demethoxycardinalin 3 (4)



SCHEME 2. Synthesis of Alkyne 7



11 12 13 14 7

constructed. Our retrosynthetic route to demethoxycardinalin 3 (**4**) is shown in Scheme 1.

Demethoxycardinalin 3 (**4**) can be synthesized from dimeric diol **5** through the oxa-Pictet−Spengler reaction (Scheme 1). Compound **5** can be obtained by a bidirectional Dötz benzannulation reaction of dimeric Fischer carbene **6** with the alkyne **7**. Carbene **6** can be derived from the biaryl compound **8**. The synthetic strategy further extends to the actual synthesis of (−)-cardinalin 3 (**3**) upon use of the axially chiral biaryl compound (*S*)-**9** to afford the chiral dimeric Fischer carbene (*S*)-**10**, which can eventually lead to natural (−)-cardinalin 3 (**3**, Scheme 1).

The synthesis of alkyne **7** is shown in Scheme 2. The known β-hydroxyester **12** was prepared by reduction of β-ketoester **11** with Baker's yeast[13] or by hydrogenation using modified Nyori catalyst by Mashima et al.[14] The latter provided **12** in quantitative yield and excellent enantioselectivity (99% ee). Protection of β-hydroxy group as TBDMS ether to **13** (98%) followed by DIBAL-H reduction of the ester group gave the aldehyde **14** (97%), which was immediately used in the Corey−Fuchs[15] procedure to obtain the alkyne **7** (80%).

The dimeric Fischer carbene **6** was prepared as shown in Table 1. Commercially available 2,2′-dihydroxybiphenyl was converted into 3,3′-dibromo-2,2′-dimethoxybiphenyl **8** following literature procedure.[16] The reaction of dibromobiaryl compound **8** with *n*-BuLi at room temperature followed by treatment with $Cr(CO)_6$ and then Me_3OBF_4 resulted in the dimeric Fischer carbene **6** in 27% yield (entry 1, Table 1). The same reaction at 0 °C gave an improved yield of **6** (36%, entry 2). However, the generation of bis-lithiated intermediate at −78 °C and sequential reaction with $Cr(CO)_6$ and then Me_3OBF_4 provided **6** in 49% yield (entry 3). When the solvent was changed to ether the reaction at room temperature provided **6** in 41% yield (entry 4) and at 0 °C in 44% yield (entry 5). Notably, the generation of bis-lithiated

(13) Hayakawa, R.; Nozawa, K.; Kimura, K.; Shimizu, M. *Tetrahedron* **1999**, *55*, 7519–7528. Variable results were obtained depending on the lot of yeast purchased from local market. In the best case, we obtained compound **12** in 69% yield and 92% ee.

(14) Mashima, K.; Nakamura, T.; Matsuo, Y.; Tani, K. *J. Organomet. Chem.* **2000**, *607*, 51–56.

(15) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

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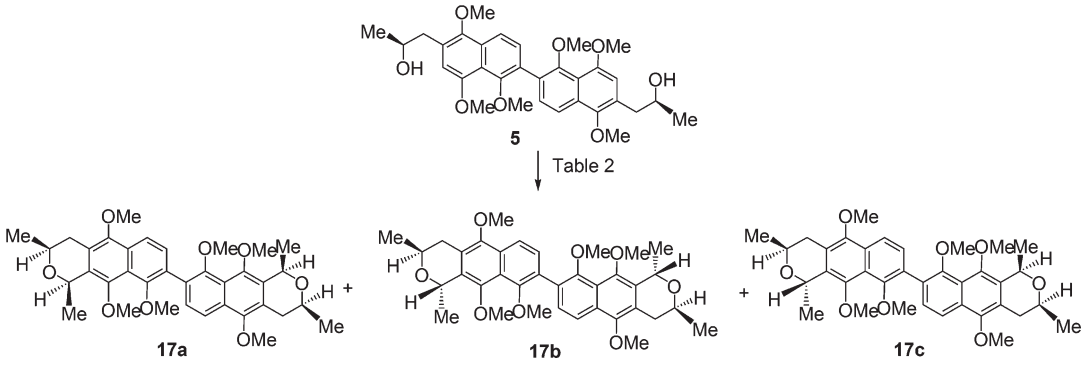
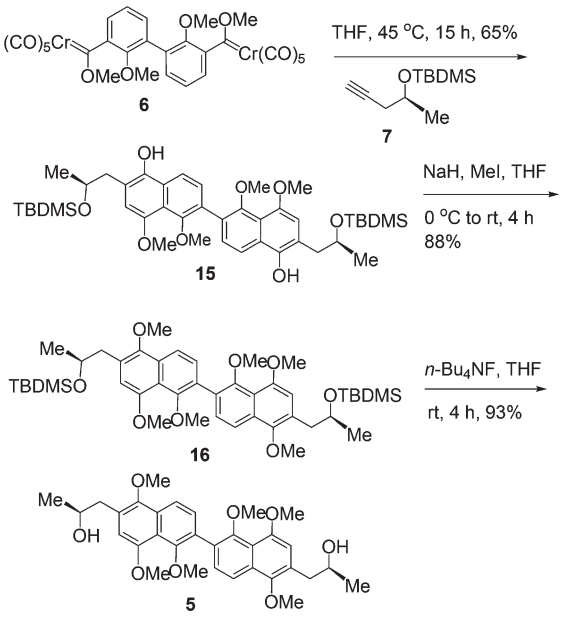
TABLE 2. The Oxa-Pictet–Spengler Reaction of Dimeric Diol 5



entry	reaction conditions	% isolated yields 17a	17b	17c[17]
1	$(CH_3O)_2CHCH_3$ (6.0 equiv), $BF_3\cdot OEt_2$ (8.0 equiv), THF, rt, 48 h		11	5
2	$(CH_3O)_2CHCH_3$ (6.0 equiv), $BF_3\cdot OEt_2$ (8.0 equiv), Et_2O, rt, 48 h		20	11
3	$(CH_3O)_2CHCH_3$ (6.0 equiv), $BF_3\cdot OEt_2$, (8.0 equiv), THF/Et_2O (1:4), rt, 24 h		41	26
4	$(CH_3O)_2CHCH_3$ (4.0 equiv), $BF_3\cdot OEt_2$, (6.0 equiv), THF/Et_2O (1:4), 0 °C, 36 h		23	15
5	$(CH_3O)_2CHCH_3$ (6.0 equiv), $BF_3\cdot OEt_2$, (8.0 equiv), CH_2Cl_2, −50 °C,1 h, 0 °C, 30 h		51	27
6	$(CH_3O)_2CHCH_3$ (6.0 equiv), $BF_3\cdot OEt_2$, (8.0 equiv), CH_2Cl_2, 0 °C, 1 h, rt, 24 h		59	23
7	$(CH_3O)_2CHCH_3$ (10.0 equiv), HCl gas, Et_2O, rt, 24 h	55		22

SCHEME 3. Synthesis of Dimeric Diol 5



intermediate at −78 °C in ether and further reactions with $Cr(CO)_6$ and then Me_3OBF_4 afforded **6** in an acceptable yield of 58% (entry 6).

With the dimeric Fischer carbene **6** in hand, our next step was to attempt the bidirectional Dötz benzannulation reaction. The Dötz benzannulation reaction of the dimeric Fischer carbene **6** with the alkyne **7** afforded the dimer **15** in good yields (65%, Scheme 3). The phenolic hydroxyl group was converted into the methyl ether to provide **16** (88%). Removal of TBDMS group in **16** gave the dimeric diol **5** (93%). Further, the pyran rings were installed using the oxa-Pictet–Spengler reaction. The optimization study is given in Table 2.

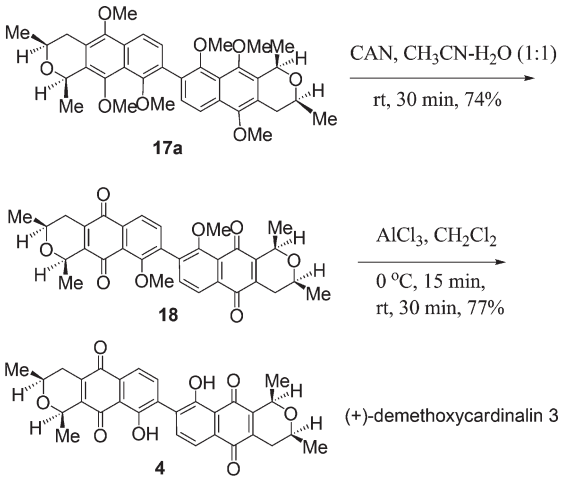
The oxa-Pictet–Spengler reaction of dimeric diol **5** with acetaldehyde dimethyl acetal was expected to give three products: **17a** (with both *syn*-1,3-dimethylpyran rings), **17b** (with both *anti*-1,3-dimethylpyran rings), and **17c** (with one *syn*- and other *anti*-1,3-dimethylpyran ring). Initial reaction of **5** with acetaldehyde dimethyl acetal and $BF_3\cdot OEt_2$ in THF at room temperature provided **17b** (11%) and **17c** (5%, entry 1, Table 2). The *syn*-dimer **17a** was not obtained. The reaction in ether (entry 2) provided **17b** (20%) and **17c** (11%). In THF/ether (1:4) solvent mixture (entry 3) at room temperature over 24 h it provided **17b** (41%) and **17c** (26%). It was our experience in the synthesis of eleutherin[9b] that at lower temperature and shorter reaction time the formation of the *syn*-1,3-dimethylpyran ring was possible. The reaction at 0 °C (entry 4) was monitored by TLC, and after 6 h, no product formation was observed. After 36 h, when compound **5** was consumed, it gave only **17b** (23%) and **17c** (15%) and **17a** was not obtained. The reaction when carried out in CH_2Cl_2 at −50 °C (entry 5) provided improved yields of **17b** (51%) and **17c** (27%). A marginal change in yield was observed when the reaction was carried out in CH_2Cl_2 at 0 °C [**17b** (59%) and **17c** (23%), entry 6]. Since in all of the above conditions compound **17a** could not be obtained, we resorted to the literature[12b,d] precedent of bubbling dry HCl gas to obtain the *syn*-1,3-dimethylpyran rings (entry 7). Overwhelmingly, this provided **17a** (55%) and **17c** (22%) with no isolation of compound **17b**. The formation of diastereomer mixtures indicates that equilibrium exists between *syn*–*anti* pyran products. Probably in the Lewis acid mediated reactions the *anti*-pyran product arises through the formation of *Z*-oxocarbenium ion and ring closure. While in the protonic catalysis it must be the *E*-oxocarbenium ion involved predominantly.[18]

The separated *syn*-dimer **17a** was converted into the corresponding quinone **18** (74%) by oxidation with cerium(IV)

(17) The structure of **17c** was arrived by the fact that it showed a different R_f value on TLC and separated clearly from the mixture of **17a**–**c** in HPLC on a C18 column (see the Supporting Information). Since it had characteristic ^1H and ^{13}C NMR peaks of both **17a** and **17b** we concluded it to have one *syn*-1,3-dimethylpyran ring and one *anti*-1,3-dimethyl pyran ring.

(18) Eid, C. N.; Shim, J.; Bikker, J.; Lin, M. *J. Org. Chem.* **2009**, *74*, 423–426.

SCHEME 4. Synthesis of (+)-Demethoxycardinalin 3 (4)



ammonium nitrate (CAN). Further demethylation with $AlCl_3$ cleanly provided (+)-demethoxycardinalin 3 (**4**, Scheme 4) in 77% yield: mp 225−227 °C; $[\alpha]^{25}_D$ +199.6 (*c* 0.32, $CHCl_3$).

In summary, we have demonstrated the synthesis of dimeric Fischer carbene and its use in the bidirectional Dötz benzannulation reaction to afford the dimeric naphthalene unit and the oxa-Pictet−Spengler reaction to install the pyran rings. Thus, we completed the stereoselective synthesis of (+)-demethoxycardinalin 3 (**4**) in seven steps from the known compound **8** and 7% overall yield. The present work further extends the use of this strategy to the actual synthesis of cardinalin 3 with the proper substituents in the axially chiral biaryl rings.

Experimental Section

(2*S*,2′*S*)-1,1′-(1,1′,5,5′,8,8′-Hexamethoxy-2,2′-binaphthyl-6,6′-diyl)dipropan-2-ol (5). To a solution of **16** (0.35 g, 0.45 mmol) in dry THF (15 mL) was added TBAF (1.13 mL, 1.13 mmol, 2.5 equiv, 1 M solution in THF) at room temperature and the mixture stirred for 4 h. It was then quenched with water (5 mL) and stirred for 30 min. THF was removed under reduced pressure and the aqueous layer extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:1 to 1:1) as eluent to give **5** (0.23 g, 93%) as a yellow solid: mp 207−208 °C; $[\alpha]^{25}_D$ = +33.8 (*c* = 1.4, $CHCl_3$); IR ($CHCl_3$) ν = 3404, 2953, 2928, 1571, 1458, 1381, 1333, 1276, 1240, 1193, 1138, 1051, 1012, 976, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.34 (d, *J* = 6.1 Hz, 6H), 2.28 (bs, 2H, OH), 2.96 (d, *J* = 6.1 Hz, 4H), 3.57 (s, 6H), 3.93 (s, 6H), 3.98 (s, 6H), 4.18−4.23 (m, 2H), 6.70 (s, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.4, 40.3, 56.4, 61.6, 61.8, 68.6, 108.3, 117.3, 120.6, 127.0, 129.1, 130.7, 131.0, 147.7, 152.8, 154.1; HRMS (ESI+) calcd for $[C_{32}H_{38}O_8 + H]^+$ 551.2645, found 551.2640.

(1*R*,1′*R*,3*S*,3′*S*)-5,5′,9,9′,10,10′-Hexamethoxy-1,1′,3,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-bibenzo[*g*]isochromene (17a). To a stirred solution of the diol **5** (100 mg, 0.18 mmol) in dry ether (15 mL) was added $(CH_3O)_2CHCH_3$ (164 mg, 1.8 mmol, 10.0 equiv), and dry HCl gas was bubbled through the mixture at room temperature for 1 h. The mixture was then stirred at room temperature for 23 h. The solvent was evaporated, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to give **17a** (60.2 mg, 55%) as a white solid. Further elution gave **17c** (24.1 mg, 22%) as a white solid. Data for **17a**: mp 255−257 °C; $[\alpha]^{25}_D$ = −52.06 (*c* = 0.76, $CHCl_3$); IR ($CHCl_3$) ν = 2970, 2931, 2841, 1668, 1595, 1552, 1446, 1384, 1357, 1329, 1217, 1160, 1132, 1077, 1047, 1017, 989, 828, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.45 (d, *J* = 6.1 Hz, 6H), 1.71 (d, *J* = 6.4 Hz, 6H), 2.63 (dd, *J* = 15.9, 11.0 Hz, 2H), 3.12 (dd, *J* = 15.9, 1.5 Hz, 2H), 3.58 (s, 6H), 3.69−3.77 (m, 2H), 3.84 (s, 6H), 3.96 (s, 6H), 5.30 (q, *J* = 6.2 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.93 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.8, 23.1, 31.9, 61.3, 61.6, 61.8, 69.4, 71.2, 117.3, 121.7, 125.8, 129.1, 129.6, 129.65, 130.7, 148.5, 148.8, 153.0; HRMS (ESI+) calcd for $[C_{36}H_{42}O_8 + H]^+$ 603.2958, found 603.2961. Data for **17c**: see the Supporting Information.

(+)-Demethoxycardinalin 3 (4). To a solution of **18** (15 mg, 0.028 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added $AlCl_3$ (19 mg, 0.14 mmol, 5.0 equiv) in portions, and the reaction mixture was stirred for 15 min. The ice bath was removed and stirring continued at room temperature for 30 min. The reaction mixture was then quenched with water (5 mL) and then extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (9:1 to 7:3) as eluent to provide **4** (11 mg, 77%) as a yellow solid: mp 225−227 °C; $[\alpha]^{25}_D$ = +199.6 (*c* = 0.32, $CHCl_3$); IR ($CHCL_3$) ν = 3461, 2928, 2855, 1732, 1660, 1641, 1610, 1417, 1336, 1275, 1238, 1080, 1013, 852, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.46 (d, *J* = 6.4 Hz, 6H), 1.59 (d, *J* = 6.6 Hz, 6H), 2.29 (ddd, *J* = 18.8, 10.2, 4.0 Hz, 2H), 2.80 (dt, *J* = 18.8, 2.6 Hz, 2H), 3.58−3.63 (m, 2H), 4.84−4.88 (m, 2H), 7.69 (d, *J* = 7.7 Hz, 2H), 7.72 (d, *J* = 7.7 Hz, 2H), 12.54 (s, 2H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 21.1, 21.2, 30.6, 68.6, 69.7, 115.1, 118.5, 131.6, 131.7, 137.6, 144.3, 146.6, 159.1, 182.9, 189.5; HRMS (ESI+) calcd for $[C_{30}H_{26}O_8 + H]^+$ 515.1706, found 515.1705.

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Supporting Information Available: General information and experimental procedures for preparation and compound characterization data of **12**, **13**, **7**, **8**, **6**, **15**, **16**, **17b**,**c**, and **18**; copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.