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Regioselective Biomimetic Oxidative Cyclization Strategy for the Synthesis of Aryldihydronaphthalene Lignans

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A regioselective biomimetic oxidative cyclization strategy for the construction of aryldihydronaphthalene skeletons has been developed as an efficient synthetic approach to the preparation of natural 8-8-cyclic diferulic acid and canabisin D. The oxidative coupling of ethyl 5-*tert*-butylferulate catalyzed by different oxidants yielded tetrahydrofuran or dibenzylidenesuccinate-type 8-8-coupling products, which were subsequently subjected to acid-catalyzed cyclization to produce several isomeric *trans*-aryldihydronaphthalenes. The reaction mechanisms for all the cyclization reactions have also been proposed.

Introduction

8-8-Cyclic diferulic acid (**3**), a dehydro-dimer of ferulic acid (**1**), is isolated from grass cell walls and belongs to an important group of arylnaphthalene lignans (Figure 1).[1] The aryldihydronaphthalene (ADHN) carbon skeleton in **3** is useful for preparing various tetralin or naphthalene lignans through further structural modifications. The synthesis of 8-8-cyclic diferulic acid and its derivatives containing the ADHN framework, including dimethyl diferulate (**4**) and canabisin D (**5**), has received considerable attention in recent decades because of their novel architectures and diverse biological activities.[2]

The biomimetic oxidative coupling of ferulic acid is the most convenient method for synthesizing various diferulic acids, including 5-5-, 8-8-, 8-5-, and 8-*O*-4-coupled dehydrodimers. However, there have only been a few reports of the successful biosynthesis of **3** by coupling reactions of **1** under various oxidative conditions.[3] Even the 8-8-coupled diester **4** has not been obtained directly from the biomimetic oxidation of methyl ferulate (**2**) because of insufficient regioselectivity at the coupling sites, with an 8-5-coupled benzofuran-type dimer predominantly being formed.[4] However, several practical routes can still be considered for the construction of ADHN skeletons, as shown in Scheme 1. Diacids **3** or **3a** can be prepared by completing a two-step reaction involving the $FeCl_3/O_2$ oxidation of **1** or sinapic acid (**1a**) and the acid-catalyzed rearrangement

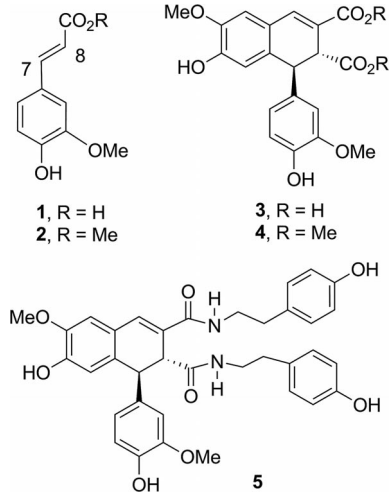

Figure 1. Ferulic acid (**1**) and its dimeric ADHN lignans **3**–**5**.

of the corresponding dilactone products **I** or **Ia** (route A).[5] The ferric chloride hydrate or horseradish peroxidase (HRP)/H_2O_2 oxidation of the esters **2a**–**2c** effectively provide the ADHN-type coupling dimers **4a**–**4c** in one step (route B) when the highly reactive C-5 position of **2** is occupied by OMe, Br, or I groups.[6] Diesters **4a**–**4c** can also be prepared by treating the dilactones **Ia**–**Ic** with methanolic hydrogen chloride at reflux (route C).[4b,7] Other 8-8-coupled lignan structures, except the dilactones, can be easily rearranged to the ADHN skeleton. Charlton and co-workers developed the cyclization of dibenzylidenesuccinates **II** to their corresponding *cis*- or *trans*-ADHN products **IV** under photochemical or acid-catalyzed conditions (route D),[8] and Wallis and co-workers realized the isomerization of diaryltetrahydrofurans **III** to *trans*-ADHN structures **IV** by using perchloric acid in acetic acid (route E).[9] A comparison of the above approaches used to obtain

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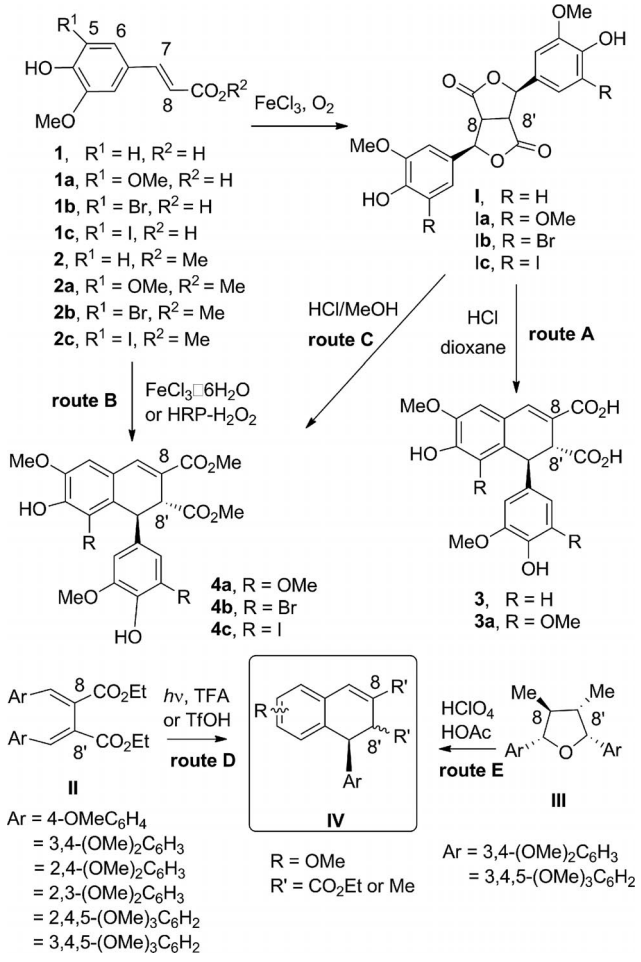
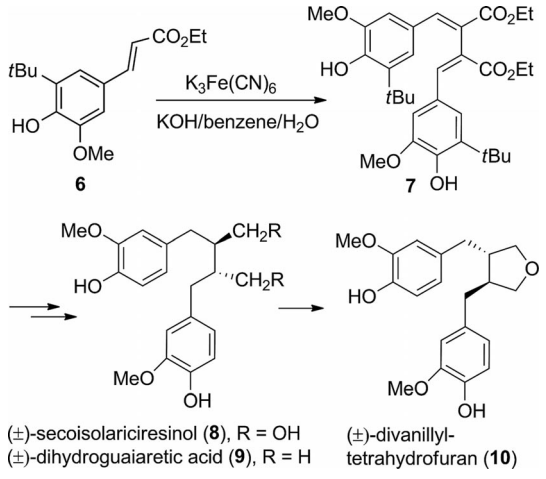
ADHN lignans showed that the regioselective biomimetic oxidative coupling of 5-substituted methyl ferulates (route B) is the most concise method.



Scheme 1. Synthetic routes to the ADHN skeletons.

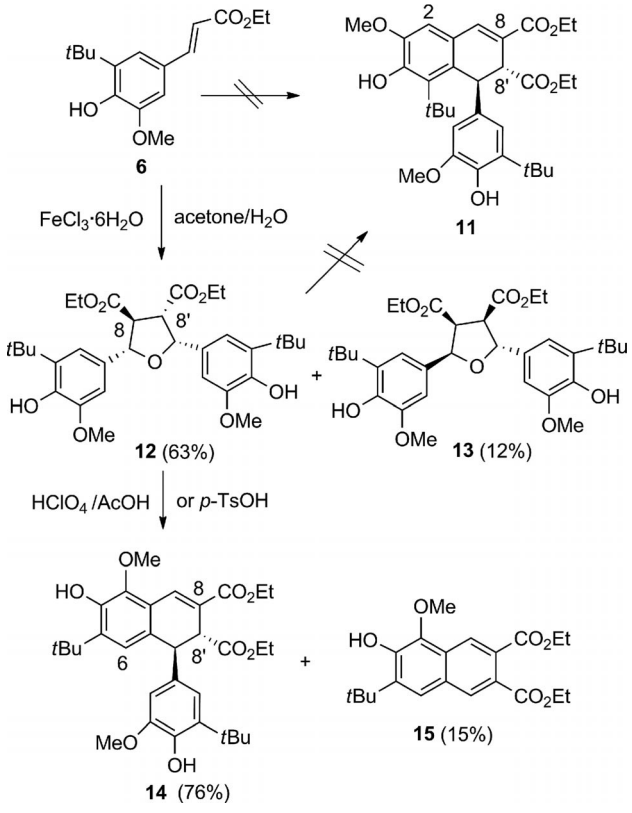
Hou and co-workers synthesized dibenzylbutane-type lignans **8**–**10** by the oxidative coupling of ethyl 5-*tert*-butylferulate (**6**) as the first step (Scheme 2)[10] and the results of route B suggest that the oxidation of **6** with ferric chloride may lead to the formation of the ADHN skeleton. Accordingly, the synthesis of natural ADHN lignans **3** and **5** has been explored by employing the oxidative coupling of **6** promoted by ferric chloride hydrate as the key step.



Scheme 2. Strategy for the synthesis of dibenzylbutane-type lignans.

Results and Discussion

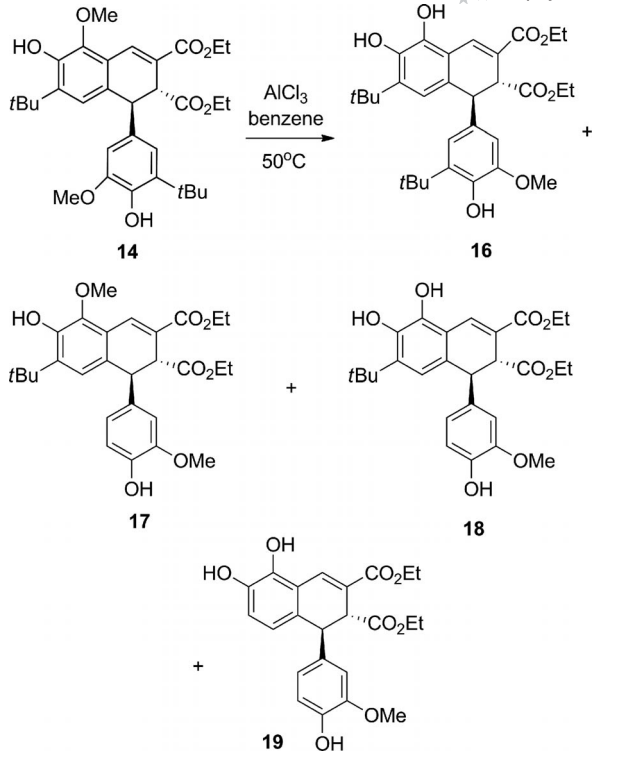
The coupling precursor **6** was prepared following the procedures of Hou and co-workers.[10a] Ferulate **6** was subjected to oxidative coupling by using ferric chloride in aqueous acetone at room temperature (Scheme 3). However, the regioselective 8-8-coupling did not yield the desired ADHN-type dimer **11**. Instead, two diastereoisomeric tetrahydrofuran products, namely, the *trans*,*trans*,*cis* isomer **12** and the *cis*,*cis*,*trans* isomer **13**, were produced with the *trans*,*trans*,*cis* isomer the predominant species. The relative configurations of these products were deduced from the coupling constants between the four methine protons and by comparison with the NMR spectroscopic data of (±)-veraguensin and its isomers.[9] This unexpected result has been attributed to the steric hindrance effects of the bulky *tert*-butyl groups on cyclization at the C-6 position, as shown by Stevenson and co-workers in their study on the oxidation products of methyl dibromoferulate.[7] The $AlCl_3$-catalyzed removal of the *tert*-butyl protecting groups from **12** was attempted, but failed because of the formation of complex unidentifiable products.



Scheme 3. $FeCl_3$-oxidized coupling of **6** and subsequent acid-catalyzed cyclization.

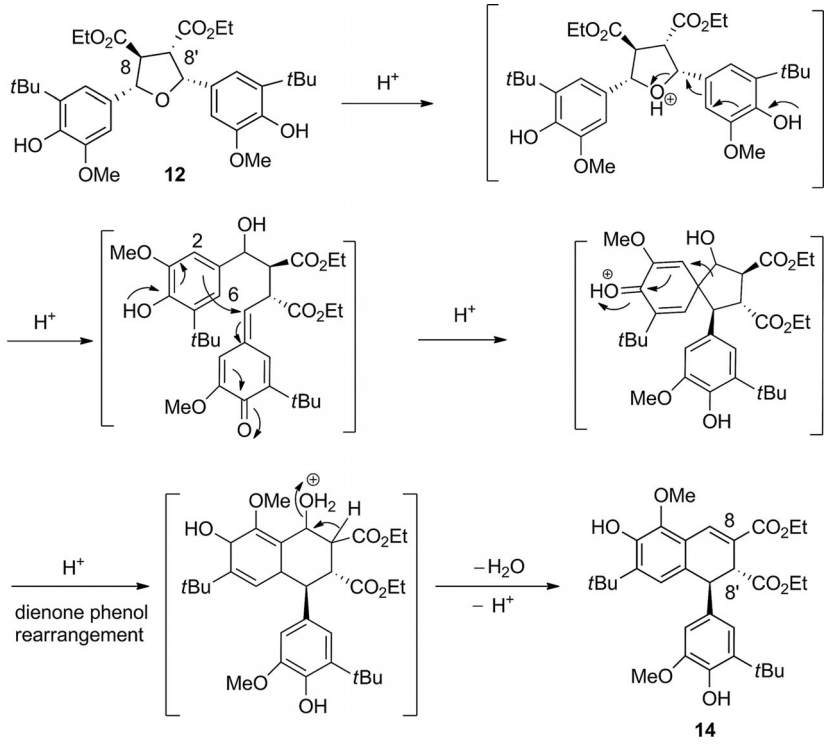
The acid-catalyzed isomerization of **12** into the target ADHN-type dimer **11** was attempted owing to the feasible conversion of tetrahydrofuran structures into the ADHN skeleton through route E of Scheme 1. Compound **12** was treated with either perchloric acid in acetic acid at room temperature or *p*-toluenesulfonic acid in toluene under reflux. ADHN **14**, which is not usually formed as a major product, was produced along with a small amount of dearylated product **15**.[8] The amount of ADHN produced significantly decreased with excess of acid or extension of the reaction time along with an increase in the dearylated product. The structure of **14**, particularly the relative positions of the substituents on the naphthalene, was confirmed by a NOE difference experiment. Ring closure was indicated *ortho* to the OMe group (C-2) instead of to the *tert*-butyl group (C-6) by the key NOE correlation between 6-H and 7-H and the methyl protons of the *tert*-butyl group.

The debutylation of **14** was carried out in the presence of $AlCl_3$ and benzene at 50 °C (Scheme 4). The OMe group at the α position of naphthalene, rather than the *tert*-butyl groups, was treated prior to cleavage, resulting in the unprotected products **16**–**18**. This reaction yielded a small quantity of global debutylated product **19** when an excess of $AlCl_3$ was used. The structural assignment of ADHN **14** was thus accordingly validated.



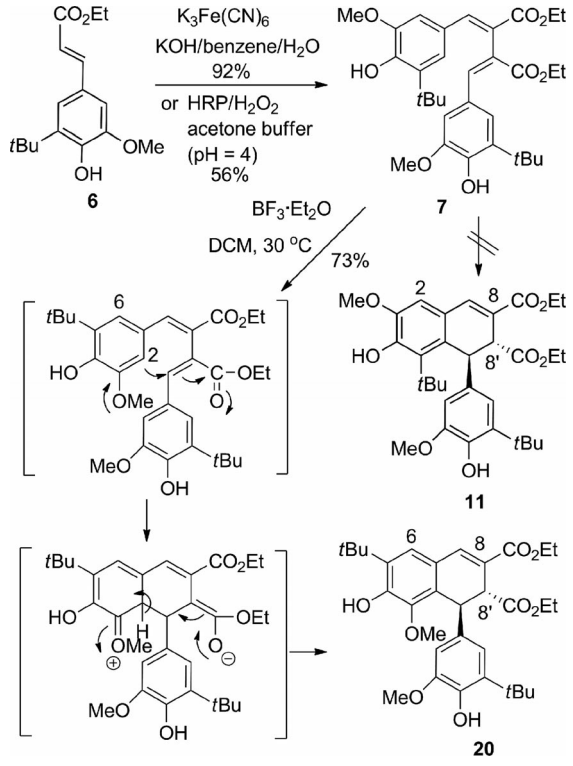
Scheme 4. Deprotection of **14**.

Scheme 5 shows a possible reaction mechanism for the acid-catalyzed transformation of **12** into **14**. The tetrahydrofuran ring in **12** is opened under acidic conditions to form a quinone methide intermediate and subsequent intramolecular nucleophilic attack provides a five-membered spiro structure. Then only the oxygen-substituted side-chain migrates in the subsequent dienone-phenol rearrangement of the spiro intermediate to yield the isomeric ADHN product from which H_2O was then eliminated to yield ADHN **14**.[11]



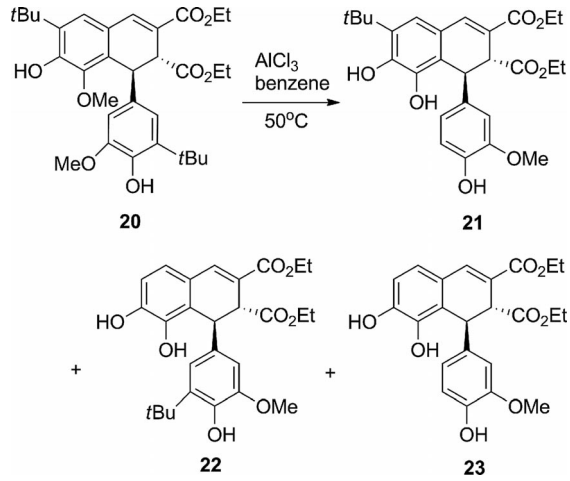
Scheme 5. Mechanism for the acid-catalyzed cyclization of **12**.

Following the above procedure, a different strategy for synthesizing dimeric intermediate **11** should be considered. Route D in Scheme 1 shows that the catalytic cyclization of dibenzylidenesuccinates **II** into ADHN skeletons is achievable. Previous work proved that dibenzylidenesuccinate **7** can be easily prepared in excellent yield by the oxidative coupling of ethyl 5-*tert*-butylferulate (**6**) in alkaline potassium ferricyanide (Scheme 2).[10a] Thus, an alternative strategy for the regioselective oxidative cyclization of **6** is proposed in Scheme 6.



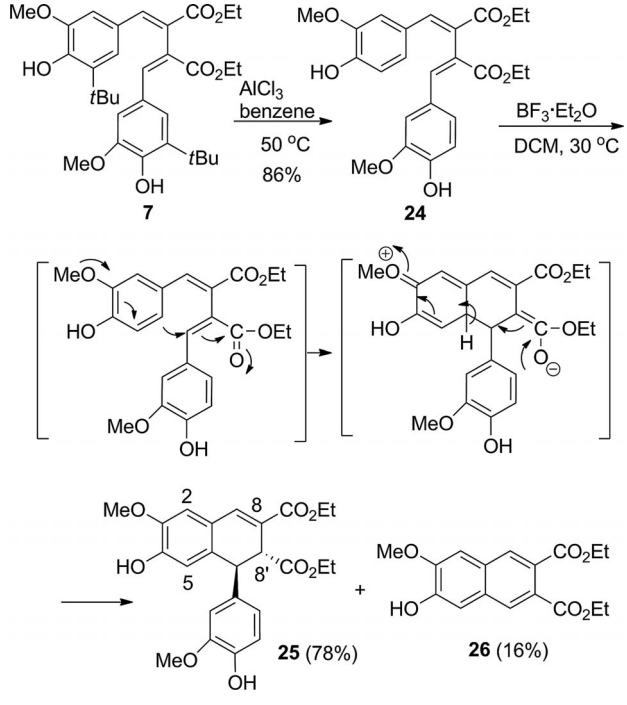
Scheme 6. $K_3Fe(CN)_6$ or HRP-promoted oxidative coupling of **6** and subsequent acid-catalyzed cyclization.

The acyclic 8-8 coupling product **7** was prepared from precursor **6** either under alkaline potassium ferricyanide oxidative conditions or by using an acidic HRP/H_2O_2 catalytic system at pH 4. The yield of **7** prepared by using the acidic catalytic system was significantly lower than that obtained under alkaline potassium ferricyanide oxidative conditions. The subsequent Lewis acid catalyzed cyclization of **7** was performed with $BF_3{\cdot}Et_2O$ and dichloromethane at 30 °C. Cyclization was more favorable *ortho* to the OMe group (C-2) than at the *para* position (C-6). Another isomeric ADHN compound, **20**, was obtained instead of **7**. The large *tert*-butyl substituent evidently blocks the ring closure at the C-6 position as originally expected. The structure of the isomeric ADHN **20** was validated by the key NOE correlation between 6-H and 7-H and the methyl protons of the *tert*-butyl group. The *trans* configuration of **20** was deduced from the small coupling constants between 7′-H and 8′-H ($J < 1.0$ Hz). Additional structural confirmation was obtained by removing the *tert*-butyl protecting groups from **20** to give compounds **21**–**23** (Scheme 7).



Scheme 7. Debutylation products of **20**.

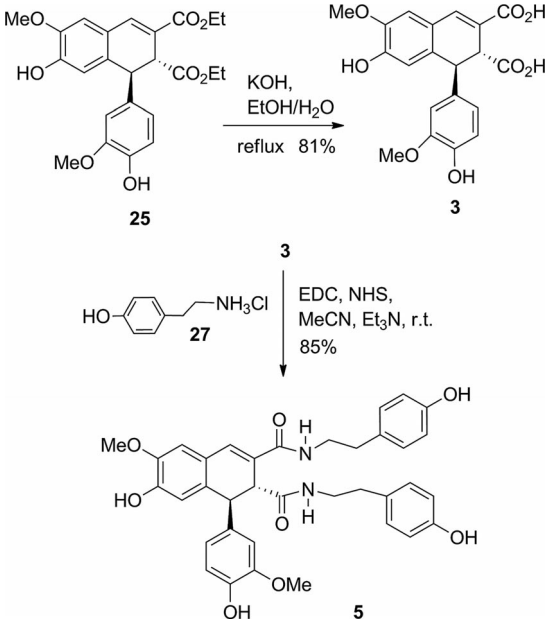
The above results predict that the desired ADHN lignan structure can be achieved by using the same cyclization reaction only if the interference by the *tert*-butyl groups at the ring closure position is eliminated. Scheme 8 shows that the *tert*-butyl groups of dibenzylidenesuccinate **7** can be easily removed to yield diethyl 8-8-open diferulate **24**.[10a,12] $BF_3{\cdot}Et_2O$-catalyzed cyclization of **24** was conducted in dichloromethane for 1 h and yielded the desired *trans*-ADHN structure **25** and a small quantity of dearylated product **26**.[13] Ring closure occurred regioselectively *para* to the OMe group (C-6) as a result of lower steric effects.



Scheme 8. Mechanism for the $BF_3{\cdot}Et_2O$-catalyzed cyclization of **24**.

The natural ADHN-type lignan **3** and lignanamide **5** can be synthesized from the *trans*-ADHN structure **25**. The diferulate **25** was subjected to alkaline hydrolysis to yield the 8-8-cyclic diferulic acid **3** (Scheme 9), which was previously

synthesized by Ralph et al. in 1994 by isomeric rearrangement of dehydrodiferulic acid dilactone. All the spectroscopic data of the prepared **3** agreed with the literature values.[1] The 8-8-cyclic diferulic acid, which is considered an important synthetic intermediate, was easily derivatized to generate various natural ADHN lignans, including lignanamide **5**. When **3** was catalytically condensed with tyramine hydrochloride (**27**) in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS), canabisin D (**5**) was obtained as a single product in 85% yield. The *trans* orientation of 7′-H and 8′-H in **5** was retained in this process, in contrast with the *cis*-**5** synthesized by the direct oxidative coupling of *N*-*trans*-feruloyltyramine catalyzed by HRP/H_2O_2 or $Cu(NO_3)_2{\cdot}3H_2O$.[2e]



Scheme 9. Synthesis of **3** and **5**.

Conclusions

An efficient synthetic approach to aryldihydronaphthalene lignans by a regioselective biomimetic oxidative cyclization strategy has been developed. Introducing the bulky *tert*-butyl groups into the coupling precursor **6** dominated the formation of 8-8-coupled tetrahydrofuran- or dibenzylidenesuccinate-type products under different oxidative conditions and considerably influenced the cyclization pathways of subsequent acid-catalyzed rearrangements of the coupled dimers. The synthesis of 8-8-cyclic diferulic acid **3** from precursor **6** was achieved in an overall yield of 50% in four steps involving oxidative coupling, debutylation, cyclization, and hydrolysis. (±)-Canabisin D was finally prepared in good yield by condensing the 8-8-cyclic diferulic acid **3** with tyramine hydrochloride. The use of this strategy for the synthesis of various naturally occurring tetralin and naphthalene lignans is currently being investigated in our laboratory.

Experimental Section

General: Structural determinations of the isolated compounds were based on ^{1}H, ^{13}C NMR, NOESY, ^{1}H-^{1}H COSY, HMBC, and HRMS analysis. All NMR spectra were recorded with a Varian Mercury 400 MHz instrument in the solvent indicated. HRMS spectra were recorded with an Autostec-3090 mass spectrometer. All solvents were freshly purified and dried by standard techniques prior to use. The products were purified by column chromatography (CC) on silica gel (200–300 mesh) purchased from QingDao Marine Chemical Co. (QingDao, China).

Diethyl 2,5-Bis(4-hydroxy-3-methoxy-5-*tert*-butylphenyl)tetrahydrofuran-3,4-dicarboxylate (12 and 13): $FeCl_3{\cdot}6H_2O$ (1.8 g, 4.76 mmol) was dissolved in water (80 mL) and slowly added to a solution of ester **6** (0.82 g, 2.95 mmol) in acetone (120 mL). The reaction mixture was stirred at room temperature under argon for 3 d. After the removal of the acetone under reduced pressure, the resulting residue was extracted with EtOAc three times. The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and the solvents evaporated in vacuo. The crude products were subjected to silica gel column chromatography (petroleum ether/EtOAc = 8:1) to give dimer **12** (0.50 g, 63%) and **13** (85 mg, 12%) as pale-yellow powders.

Major Product **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.81 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.22 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.36 [s, 9 H, $(CH_3)_3$], 1.42 [s, 9 H, $(CH_3)_3$], 3.55–3.62 (m, 1 H, $OCHCH_3$), 3.68 (dd, *J* = 8.4, 2.4 Hz, 1 H, 8′-H), 3.67–3.78 (m, 2 H, 8-H, $OCHCH_3$), 3.86 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.11–4.23 (m, 2 H, OCH_2CH_3), 4.96 (d, *J* = 8.4 Hz, 1 H, 7′-H), 5.26 (d, *J* = 8.0 Hz, 1 H, 7-H), 5.96 (s, 1 H, OH), 6.03 (s, 1 H, OH), 6.81 (d, *J* = 1.6 Hz, 1 H, 2-H), 6.92 (d, *J* = 1.6 Hz, 1 H, 6-H), 7.06 (d, *J* = 1.6 Hz, 1 H, 2′-H), 7.15 (d, *J* = 1.6 Hz, 1 H, 6′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.6, 14.2, 29.3 (6 C), 34.6 (2 C), 54.7, 54.9, 56.1 (2 C), 60.6, 61.1, 82.8, 84.0, 107.0 (2 C), 117.6, 118.1, 127.7, 129.8, 134.9 (2 C), 144.0, 144.3, 146.2, 146.7, 171.4, 172.4 ppm. HRMS (ESI): calcd. for $C_{32}H_{44}O_9 + NH_4$ 590.3324; found 590.3316.

Minor Product **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.85 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.21 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.36 [s, 9 H, $(CH_3)_3$], 1.40 [s, 9 H, $(CH_3)_3$], 3.47 (dd, *J* = 8.8, 7.2 Hz, 1 H, 8′-H), 3.68–3.81 (m, 3 H, 8-H, OCH_2CH_3), 3.87 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.06–4.19 (m, 2 H, OCH_2CH_3), 5.58 (d, *J* = 6.0 Hz, 1 H, 7′-H), 5.83 (d, *J* = 8.8 Hz, 1 H, 7-H), 5.96 (s, 1 H, OH), 5.97 (s, 1 H, OH), 6.86 (d, *J* = 1.6 Hz, 1 H, 2′-H), 6.88 (d, *J* = 1.6 Hz, 1 H, 2-H), 6.96 (d, *J* = 1.6 Hz, 1 H, 6′-H), 7.07 (d, *J* = 1.6 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 13.7, 14.0, 29.4 (6 C), 31.8, 34.6, 55.0, 56.2 (3 C), 60.4, 60.9, 81.7, 83.3, 106.3, 106.5, 116.8 (2 C), 117.0 (2 C), 127.9, 133.0, 135.0, 135.3, 143.8 (2 C), 146.4, 146.6, 170.3, 170.5 ppm. HRMS (ESI): calcd. for $C_{32}H_{44}O_9 + NH_4$ 590.3324; found 590.3318.

Diethyl 6-Hydroxy-1-(4-hydroxy-3-methoxy-5-*tert*-butylphenyl)-5-methoxy-7-*tert*-butyl-1,2-dihydronaphthalene-2,3-dicarboxylate (14): Compound **12** (280 mg, 0.5 mmol) was dissolved in acetic acid (20 mL) containing 16% perchloric acid (5 mL) and was kept at room temperature for 8 h. After neutralization with a saturated solution of $NaHCO_3$, the reaction mixture was extracted with EtOAc and the extract was washed with brine and dried with anhydrous $MgSO_4$. The solvent was evaporated in vacuo and the crude products were subjected to silica gel column chromatography (petroleum ether/EtOAc = 8:1) to give **14** (200 mg, 76%) and **15** (27 mg, 15%) as pale-white powders.

Major Product **14**: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.12 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.29 [s, 9 H, $(CH_3)_3$], 1.31 (t, *J* = 7.2 Hz,

3 H, OCH_2CH_3), 1.38 [s, 9 H, $(CH_3)_3$], 3.75 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.06 (d, J = 3.2 Hz, 1 H, 8′-H), 4.07 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.24 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.52 (d, J = 3.2 Hz, 1 H, 7′-H), 5.84 (s, 1 H, OH), 5.97 (s, 1 H, OH), 6.42 (d, J = 1.2 Hz, 1 H, 2′-H), 6.55 (d, J = 1.2 Hz, 1 H, 6′-H), 6.81 (s, 1 H, 6-H), 7.87 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.0, 14.3, 29.3 (6 C), 34.7, 35.1, 46.0, 47.3, 56.0, 60.8, 60.9, 63.2, 107.8 (2 C), 118.4 (2 C), 121.9, 122.9 (2 C), 125.7, 128.5, 130.9, 132.8, 135.0, 138.7, 142.8, 144.9, 146.3, 166.6, 172.4 ppm. HRMS (ESI): calcd. for $C_{32}H_{42}O_8$ + H 555.2952; found 555.2957.

Minor Product **15**: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.39 (t, J = 7.2 Hz, 6 H, OCH_2CH_3), 1.49 [s, 9 H, $(CH_3)_3$], 1.31 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 3.98 (s, 3 H, OCH_3), 4.37–4.45 (m, 4 H, OCH_2CH_3), 6.45 (s, 1 H, OH), 7.60 (s, 1 H, 6-H), 8.17 (s, 1 H, 7-H), 8.23 (s, 1 H, 7′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.1, 14.2, 29.4 (3 C), 35.6, 61.4, 61.6, 62.2, 121.6, 122.3, 125.8, 126.2, 128.1, 129.4, 131.0, 140.6, 141.3, 148.1, 167.6, 168.5 ppm. HRMS (ESI): calcd. for $C_{21}H_{26}O_6$ + Na 397.1622; found 397.1630.

Deprotected Products of 14: $AlCl_3$ (8 equiv., 144 mg) was added to a solution of compound **14** (100 mg, 0.18 mmol) in benzene (10 mL) at 50 °C. The mixture was stirred at this temperature for 1 h and then the reaction was quenched with ice and extracted with benzene (3 × 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and the solvents evaporated in vacuo. The residue was purified by column chromatography using petroleum ether and ethyl acetate (6:1, v/v) as eluent to afford **16** (6 mg, 6%), **17** (17 mg, 19%), **18** (20 mg, 23%), and **19** (6 mg, 8%) as pale-yellow powders.

16: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.07 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.25 [s, 9 H, $(CH_3)_3$], 1.23 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.29 [s, 9 H, $(CH_3)_3$], 3.67 (s, 3 H, OCH_3), 3.97–4.07 (m, 2 H, OCH_2CH_3), 4.01 (d, J = 3.6 Hz, 1 H, 8′-H), 4.11–4.21 (m, 2 H, OCH_2CH_3), 4.46 (d, J = 3.6 Hz, 1 H, 7′-H), 5.44 (s, 1 H, OH), 5.77 (s, 2 H, OH), 6.34 (d, J = 1.2 Hz, 1 H, 2′-H), 6.54 (d, J = 1.2 Hz, 1 H, 6′-H), 6.60 (s, 1 H, 6-H), 7.88 (s, 1 H, 7-H) ppm. HRMS (ESI): calcd. for $C_{21}H_{26}O_6$ + Na 563.2615; found 563.2599.

17: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.18 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.30 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.33 [s, 9 H, $(CH_3)_3$], 3.79 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.00 (d, J = 3.2 Hz, 1 H, 8′-H), 4.04–4.13 (m, 2 H, OCH_2CH_3), 4.18–4.27 (m, 2 H, OCH_2CH_3), 4.55 (d, J = 3.2 Hz, 1 H, 7′-H), 5.47 (s, 1 H, OH), 5.97 (s, 1 H, OH), 6.43 (dd, J = 8.0, 2.0 Hz, 1 H, 6′-H), 6.57 (d, J = 2.0 Hz, 1 H, 2′-H), 6.74 (d, J = 8.0 Hz, 1 H, 5′-H), 6.78 (s, 1 H, 6-H), 7.88 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.0, 14.2, 29.3, 35.1, 45.8, 47.6, 55.8, 60.8, 60.9, 63.2, 110.3, 114.1, 120.5, 122.0, 122.8, 125.3, 128.0, 131.1, 134.7, 138.8, 144.3, 144.8, 146.3, 146.5, 166.6, 172.3 ppm. HRMS (ESI): calcd. for $C_{21}H_{26}O_6$ + Na 521.2146; found 521.2132.

18: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.15 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.28 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.34 [s, 9 H, $(CH_3)_3$], 3.78 (s, 3 H, OCH_3), 4.00 (d, J = 2.8 Hz, 1 H, 8′-H), 3.95–4.09 (m, 2 H, OCH_2CH_3), 4.12–4.21 (m, 2 H, OCH_2CH_3), 4.55 (d, J = 2.8 Hz, 1 H, 7′-H), 5.47 (s, 1 H, OH), 5.56 (s, 1 H, OH), 5.93 (br. s, 1 H, OH), 6.43 (dd, J = 8.0, 2.0 Hz, 1 H, 6′-H), 6.58 (d, J = 2.0 Hz, 1 H, 2′-H), 6.62 (s, 1 H, 6-H), 6.73 (d, J = 8.0 Hz, 1 H, 5′-H), 7.99 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.2, 14.4, 29.7 (3 C), 34.9, 46.1, 47.6, 56.0, 61.1, 61.3, 110.4, 114.3, 117.8, 119.7, 120.6, 124.6, 128.3, 131.0, 135.0, 138.7, 141.7, 142.4, 144.5, 146.5, 167.0, 172.6 ppm. HRMS (ESI): calcd. for $C_{27}H_{32}O_8$ + Na 507.1989; found 507.1999.

19: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.15 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.31 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 3.79 (s, 3 H, OCH_3), 4.01 (d, J = 2.8 Hz, 1 H, 8′-H), 4.04–4.14 (m, 2 H, OCH_2CH_3), 4.20–4.26 (m, 2 H, OCH_2CH_3), 4.54 (d, J = 2.8 Hz, 1 H, 7′-H), 5.47 (s, 2 H, OH), 5.84 (br. s, 1 H, OH), 6.45 (dd, J = 8.0, 2.0 Hz, 1 H, 6′-H), 6.51 (d, J = 8.0 Hz, 1 H, 5′-H), 6.61 (d, J = 2.0 Hz, 1 H, 2′-H), 6.71 (d, J = 8.0 Hz, 1 H, 6-H), 6.73 (d, J = 8.0 Hz, 1 H, 5-H), 8.08 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.1, 14.2, 45.7, 47.4, 55.9, 60.8, 61.2, 110.2, 111.3, 114.2, 116.5, 119.8, 120.4, 120.6, 124.5, 131.3, 134.6, 142.2, 142.4, 144.4, 146.4, 166.7, 172.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}O_6$ + Na 341.0996; found 341.1002.

Synthesis of Diethyl (*E*,*E*)-Bis(3-methoxy-4-hydroxy-5-*tert*-butylbenzylidene)succinate (7)

Alkaline Potassium Ferricyanide Oxidation:[10] Compound **6** (2 g, 0.72 mol) in benzene (35 mL) was vigorously stirred with an aqueous solution (25 mL) of potassium ferricyanide (7 g) and potassium hydroxide (4 g) for 0.5 h under nitrogen. The organic layer was washed with water and brine, and dried with $MgSO_4$. The solvent was evaporated in vacuo and the residue purified by column chromatography using petroleum ether and ethyl acetate (6:1, v/v) as eluent to afford **7** (1.8 g, 92%) as a yellow solid.

HRP/H_2O_2 Oxidation: HRP (10 mg, RZ > 3, activity ≥300 U/mg) was dissolved in buffer solution (pH = 4, 6 mL) and a solution of compound **6** (500 mg, 1.8 mmol) in acetone (12 mL) was added at room temperature under argon. After stirring for 10 min, the mixture was treated with hydrogen peroxide (3%, 2 mL) and stirred for a further 12 h. The reaction mixture was quenched with water and extracted with EtOAc (50 mL), washed with saturated brine, and then dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified on silica gel (petroleum ether/EtOAc = 6:1) to give pure **7** (280 mg, 56%). All the spectral data for **7** are in accord with the literature values.[10a]

Diethyl 7-Hydroxy-1-(4-hydroxy-3-methoxy-5-*tert*-butylphenyl)-8-methoxy-6-*tert*-butyl-1,2-dihydronaphthalene-2,3-dicarboxylate (20): $BF_3{\cdot}Et_2O$ (2 mL) was added to a solution of compound **7** (93 mg, 0.16 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred for 3 h at 30 °C, and then quenched with ice/water (5 mL) and extracted with EtOAc. The combined organic layers were washed with saturated brine and then dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified on silica gel (petroleum ether/EtOAc = 6:1) to afford compound **20** (68 mg, 73%) as a pale-yellow amorphous powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.18 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.28 [s, 9 H, $(CH_3)_3$], 1.32 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.39 [s, 9 H, $(CH_3)_3$], 3.69 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.04 (s, 1 H, 8′-H), 4.03–15 (m, 2 H, OCH_2CH_3), 4.19–4.25 (m, 2 H, OCH_2CH_3), 4.96 (s, 1 H, 7′-H), 5.83 (s, 1 H, OH), 6.23 (s, 1 H, OH), 6.47 (s, 1 H, 2′-H), 6.57 (s, 1 H, 6′-H), 7.06 (s, 1 H, 6-H), 7.63 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.0, 14.3, 29.3 (6 C), 34.6, 39.6, 46.1, 56.0, 60.5, 61.1, 61.6, 107.6 (2 C), 118.1 (2 C), 122.1, 123.7, 124.1, 127.7, 132.2, 134.9, 135.5, 137.7 (2 C), 142.9, 145.0, 146.3, 150.0, 166.9, 172.2 ppm. HRMS (ESI): calcd. for $C_{32}H_{42}O_8$ + H 555.2952; found 555.2959.

Deprotected Products of 20: $AlCl_3$ (8 equiv., 144 mg) was added to a solution of compound **20** (102 mg, 0.18 mmol) in benzene (10 mL) at 50 °C. The mixture was stirred at this temperature for 1 h, and then the reaction was quenched with ice and extracted with benzene. The combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (6:1, v/v) as eluent to afford a mixture of **21** and **22** (32 mg, 37%) as well as **23** (8 mg, 10%) as pale-yellow powders.

21: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.10 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.19 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.34 [s, 9 H, $(CH_3)_3$], 3.72 (s, 3 H, OCH_3), 3.93 (d, J = 1.6 Hz, 1 H, 8′-H), 3.97–4.05 (m, 2 H, OCH_2CH_3), 4.10–4.20 (m, 2 H, OCH_2CH_3), 4.74 (d, J = 1.6 Hz, 1 H, 7′-H), 5.00 (br. s, 1 H, OH), 5.47 (s, 1 H, OH), 6.02 (s, 1 H, OH), 6.42 (dd, J = 8.0, 2.0 Hz, 1 H, 6′-H), 6.59 (d, J = 2.0 Hz, 1 H, 2′-H), 6.68 (d, J = 8.0 Hz, 1 H, 5′-H), 6.89 (s, 1 H, 6-H), 7.59 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.3 (2 C), 29.4, 34.5, 47.2, 47.3, 56.0, 60.6, 61.3, 107.5, 109.9, 114.6, 118.1, 120.2, 121.6, 131.6, 132.9, 138.0, 140.4, 141.2, 143.4, 145.0, 146.9, 166.8, 172.5 ppm. HRMS (ESI): calcd. for $C_{27}H_{32}O_8$ + Na 507.1989; found 507.1996.

22: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.12 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.20 (t, J = 6.8 Hz, 3 H, OCH_2CH_3), 1.24 [s, 9 H, $(CH_3)_3$], 3.65 (s, 3 H, OCH_3), 3.96 (d, J = 2.0 Hz, 1 H, 8′-H), 4.00–4.08 (m, 4 H, OCH_2CH_3), 4.1–4.17 (m, 2 H, OCH_2CH_3), 4.55 (d, J = 2.8 Hz, 1 H, 7′-H), 5.24 (br. s, 1 H, OH), 5.79 (s, 1 H, OH), 5.91 (br. s, 1 H, OH), 6.40 (d, J = 2.0 Hz, 1 H, 6′-H), 6.63 (d, J = 2.0 Hz, 1 H, 2′-H), 6.69 (d, J = 8.0 Hz, 1 H, 5′-H), 6.81 (d, J = 8.0 Hz, 1 H, 5′-H), 7.59 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.0 (2 C), 29.3, 34.8, 44.0, 46.8, 56.0, 60.6, 61.3, 105.4, 113.8, 118.4, 121.3, 122.4, 122.8, 123.0, 129.7, 133.4, 135.2, 135.5, 137.4, 146.3, 146.4, 165.5, 171.8 ppm. HRMS (ESI): calcd. for $C_{27}H_{32}O_8$ + Na 507.1989; found 507.1996.

23: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.19 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.26 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 3.79 (s, 3 H, OCH_3), 4.01 (s, 1 H, 8′-H), 4.06–4.16 (m, 2 H, OCH_2CH_3), 4.18–4.25 (m, 2 H, OCH_2CH_3), 4.94 (s, 1 H, 7′-H), 5.36 (br. s, 1 H, OH), 5.49 (s, 2 H, OH), 6.50 (dd, J = 8.0, 2.0 Hz, 1 H, 6′-H), 6.68 (d, J = 2.0 Hz, 1 H, 2′-H), 6.73 (d, J = 8.0 Hz, 1 H, 5′-H), 6.76 (d, J = 8.0 Hz, 1 H, 6-H), 6.89 (d, J = 8.0 Hz, 1 H, 5-H), 7.66 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.2, 14.4, 39.7, 47.1, 56.0, 60.8, 61.5, 110.2, 114.1, 114.5, 120.3, 122.8, 123.8, 125.2, 131.7, 132.4, 133.5, 137.4, 141.3, 144.9, 146.7, 167.0, 172.5 ppm. HRMS (ESI): calcd. for $C_{23}H_{24}O_8$ + Na 451.1363; found 451.1372.

Diethyl 7-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-6-methoxy-1,2-dihydronaphthalene-2,3-dicarboxylate (25): $BF_3{\cdot}Et_2O$ (3 mL) was added to a solution of compound **24**[10a] (93 mg, 0.22 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred for 3 h at 30 °C, and then quenched with ice/water (5 mL) and extracted with EtOAc. The combined organic layers were washed with saturated brine and dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue purified on silica gel (petroleum ether/EtOAc = 6:1) to afford compound **25** (72 mg, 78%) and **26** (11 mg, 16%) as yellow amorphous powders.

Major Product **25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.14 (t, J = 7.2 Hz, OCH_2CH_3), 1.29 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 3.81 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.97 (d, J = 3.6 Hz, 1 H, 8′-H), 4.01–4.13 (m, 2 H, OCH_2CH_3), 4.18–4.24 (m, 2 H, OCH_2CH_3), 4.53 (d, J = 3.6 Hz, 1 H, 7′-H), 5.47 (s, 1 H, OH), 5.76 (s, 1 H, OH), 6.45 (dd, J = 8.0, 2.0 Hz, 1 H, 6′-H), 6.63 (d, J = 2.0 Hz, 1 H, 2′-H), 6.68 (s, 1 H, 5-H), 6.73 (d, J = 8.0 Hz, 1 H, 5′-H), 6.84 (s, 1 H, 2-H), 7.64 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.0, 14.2, 45.8, 47.5, 55.9, 56.1, 60.6, 61.0, 110.3, 111.2, 114.2, 115.5, 120.6, 123.2, 124.0, 131.4, 134.4, 137.2, 144.5, 145.7, 146.4, 147.6, 166.7, 172.5 ppm. HRMS (ESI): calcd. for $C_{24}H_{26}O_8$ + H 443.1700; found 443.1698.

Minor Product **26**: ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.18 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 4.05 (s, 3 H, OCH_3), 4.40 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 6.13 (s, 1 H, OH), 7.18 (s, 1 H, 5-H), 7.32 (s, 1 H, 2-H), 8.03 (s, 1 H, 7-H), 8.10 (s, 1 H, 7′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 14.2 (2 C), 56.1, 61.4, 61.5, 106.3, 110.1, 126.8, 127.7, 128.2, 128.6, 129.2, 130.1, 147.8, 149.1, 167.9, 168.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}O_6$ + Na 341.0996; found 341.1001.

8-8-Cyclic Diferulic Acid (3): An aqueous solution of KOH (200 mg, 3.6 mol) in H_2O (2 mL) was added to a solution of compound **25** (160 mg, 0.36 mmol) in ethanol (6 mL) at room temperature. The mixture was continuously stirred under reflux for 6 h and then cooled to room temperature. After the removal of ethanol in vacuo, dilute aqueous hydrochloric acid was added to the residue to achieve pH 1. The solution was extracted with diethyl ether several times and the combined organic layers were washed with brine and dried with $MgSO_4$. The solvent was evaporated in vacuo and the residue purified by column chromatography (petroleum ether/EtOAc/HOAc = 15:15:1, v/v/v) to afford **3** (110 mg, 81%) as a white amorphous powder.

^{1}H NMR (400 MHz, [D$_6$]acetone): δ_H = 3.75 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.94 (s, 1 H, 8′-H), 4.60 (s, 1 H, 7′-H), 6.40 (dd, J = 8.0, 1.6 Hz, 1 H, 6′-H), 6.63 (d, J = 8.0 Hz, 1 H, 5′-H), 671 (s, 1 H, 5-H), 6.80 (d, J = 1.6 Hz, 1 H, 2′-H), 7.09 (s, 1 H, 2-H), 7.67 (s, 1 H, 7-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ_C = 46.2, 47.7, 56.2, 56.4, 111.9, 112.0, 113.1, 113.2, 115.5, 116.9, 116.9, 120.7, 123.6, 124.6, 132.3, 135.8, 138.3, 146.1, 147.5, 148.1, 149.4 168.5, 173.5 ppm. HRMS (ESI): calcd. for $C_{20}H_{17}O_8$ – H 385.0929; found 385.0933.

(±)-Canabisin D (5): NHS (45 mg, 2.5 equiv.) was added to a solution of acid **3** (50 mg, 0.13 mmol) in dry acetonitrile (4 mL). After stirring for 5 min, EDCI (75 mg, 2.5 equiv.) was added to the mixture in an ice bath and stirred for a further 4 h until **3** was no longer detected by TLC. Tyramine hydrochloride (**27**; 65 mg, 2.5 equiv.) and triethylamine (1 mL) were then added to the reaction and the mixture stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc, washed with 5% citric acid, saturated aqueous $NaHCO_3$, and brine, and dried with $MgSO_4$. The solvent was evaporated in vacuo and the residue purified by column chromatography (dichloromethane/methanol = 25:1, v/v) to afford **5** (68 mg, 85%) as an amorphous powder.

^{1}H NMR (400 MHz, [D$_6$]acetone): δ_H = 2.54 (t, J = 7.2 Hz, 2 H, $ArCH_2$), 2.71 (t, J = 7.2 Hz, 2 H, $ArCH_2$), 3.17–3.30 (m, 2 H, $NHCH_2$), 3.41 (q, J = 6.4 Hz, 2 H, $NHCH_2$), 3.67 (s, 1 H, 8′-H), 3.74 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.59 (s, 1 H, 7′-H), 6.39 (dd, J = 8.0, 2.0 Hz, 1 H, 6′-H), 6.49 (d, J = 8.0 Hz, 1 H, 5′-H), 6.55 (s, 1 H, 5-H), 6.58 (d, J = 8.0 Hz, 2 H, 3′′-H, 5′′-H), 6.61 (d, J = 8.0 Hz, 2 H, 3′′′-H, 5′′′-H), 6.66 (d, J = 2.0 Hz, 1 H, 2′-H), 6.73 (s, 1 H, 2-H), 6.80 (d, J = 8.0 Hz, 2 H, 2′′-H, 6′′-H), 6.87 (d, J = 8.0 Hz, 2 H, 2′′′-H, 6′′′-H), 7.11 (s, 1 H, 7-H), 7.47 (q, J = 6.4 Hz, 2 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ_C = 35.5, 35.6, 42.1, 42.4, 45.5, 49.6, 56.3, 56.4, 112.2, 112.6, 115.5, 116.0 (2 C), 116.1 (2 C), 117.1, 120.9, 124.4, 127.9, 130.5 (2 C), 130.6 (3 C), 131.1, 132.6, 133.2, 136.5, 146.0, 147.3, 148.1, 149.0, 156.6, 156.7, 169.5, 171.8 ppm. HRMS (ESI): calcd. for $C_{36}H_{36}N_2O_8$ – H 623.2388; found 623.2394.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all key intermediates and final products.

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[13] Hou and co-workers reported that ADHN **25** was directly produced by treating **7** with 12 equiv. $AlCl_3$ in benzene at 50 °C for 1 h.[10a] This can be considered as a $AlCl_3$-catalyzed one-pot debutylation/cyclization reaction. However, we repeated the reaction under these experimental conditions and found it to be poorly reproducible, and thus it was difficult to accumulate enough **25** for further conversion.

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