Non-oxidative Dimerization of 3,4-Dioxygenated Cinnamates to Aryltetralin Lignans

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The BF_3 catalyzed dimerization of (*E*)-3,4-dimethoxycinnamic acid methyl ester offers a route to aryltetralin lignans. The mechanism of the reaction is discussed.

Keywords (*E*)-3,4-dimethoxycinnamic acid methyl ester; non-oxidative dimerization; aryltetralin lignan; Lewis acid; mechanism

The pharmacological interest in aryltetralin lignans is based on their cytotoxic,[1] antitumour,[2] and anti-infective[3] activities. Classical syntheses of lignans involve phenolic oxidative coupling, Diels–Alder reactions, and Stobbe condensations, while modern methods employ non-phenolic oxidative coupling, cycloaddition to quinone monoketals, and conjugate addition by acyl anion equivalents.[4] We now report a novel approach to aryltetralin lignans involving a non-oxidative dimerization of 3,4-dimethoxycinnamic acid methyl ester. It should be noted that an aryltetralin skeleton has been obtained in a one-step reaction, but the process involves oxidative coupling of methyl (*E*)-sinapate.[5] Furthermore, our approach can be applied to non-phenolic compounds as starting materials.

Results and Discussion

During studies on photodimerization of (*E*)-3,4-dimethoxycinnamic acid methyl ester (**1**), two unexpected compounds, designated as AL-A and AL-B, were obtained in a 3:1 ratio and in an overall yield of 90%, when the reaction was carried out in the presence of $BF_3 \cdot Et_2O$. The two compounds showed coincident ultraviolet (UV) and mass spectra (MS). The molecular peak was found at *m/z* 444, suggesting a dimeric molecule, since the molecular formula, $C_{24}H_{28}O_8$, established by MS, and proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectroscopy, was double that of the starting material. The NMR spectra of both compounds (Table I) exhibited characteristic signals of two carbomethoxyl and four aromatic methoxyl functions. In addition, five aromatic proton signals were observed, three of which exhibited the typical *ortho–ortho* and *meta* coupling in the spectrum of **1**, whereas the remaining two protons displayed a *para* coupling. Finally, the signals of five aliphatic protons, typical of an ABCXY system, were found.

The lowest-field aliphatic proton signals (δ 4.69 in AL-A and 4.54 in AL-B; H-1 in Table I), by virtue of their chemical

TABLE I. ^{1}H-NMR Data for AL-A (**2**) and AL-B (**3**)

Proton	AL-A		AL-B	
1	4.69 (d)	$J_{1,2}=10$	4.54 (d)	$J_{1,2}=9.5$
2	3.44 (dd)	$J_{2,3}=8$	3.03 (t)	$J_{2,3}=9.3$
3	3.98 (q)	$J_{3,4eq}=7$	3.77 (m)	$J_{3,4eq}=6$
4ax	2.47 (dd)	$J_{3,4ax}=8$	2.75 (dd)	$J_{3,4ax}=7$
4eq	2.62 (dd)	$J_{4ax,4eq}=16$	2.92 (dd)	$J_{4ax,4eq}=16$
5	6.79 (br s)		6.79 (d)	$J_{5,8}=1$
8	6.41 (br s)		6.40 (d)	
2′	6.70 (d)	$J_{2',6'}=1.5$	6.72 (d)	$J_{2',6'}=1.5$
5′	6.83 (d)	$J_{5',6'}=8$	6.84 (d)	$J_{5',6'}=8$
6′	6.79 (dd)		6.77 (dd)	
OMe	3.88, 3.89 (s)		3.89, 3.88 (s)	
	3.81, 3.73		3.83, 3.73	
COOMe	3.69, 3.65 (s)		3.71, 3.70 (s)	

In $CDCl_3$. The signals showed the appropriate integral intensities. The coupling constants (in Hz) are given only once.

TABLE II. NOE Enhancements Observed for AL-A and AL-B

Proton irradiated	Protons observed	
	AL-A	AL-B
H-1	H-2′, H-6′, H-8	H-2′, H-6′, H-3
H-2	H-3, H-2′	H-2′, H-4ax
H-8	H-1, 7-OMe (δ 3.73)	H-1, 7-OMe (δ 3.73)
H-2′	H-1, H-2, 3′-OMe (δ 3.81)	*a)*

a) Not examined.

TABLE III. Carbon Resonances and Connectivities for AL-A and AL-B

Carbon	AL-A	Long range connected carbons	AL-B
1	51.47	2, 8, 9, 10, 1′, 2′, 6′	53.64
2	58.71	—	61.16
3	42.35	2	43.92
4	36.72	5, 10	38.90
5	106.90	7, 9	106.03
6	149.16	—	149.10
7	148.96	—	149.01
8	107.84	1, 6, 10	107.71
9	135.54	—	135.65
10	135.92	—	135.95
1′	134.97	—	134.78
2′	111.27	1, 4′, 6′	111.23
3′	148.66	—	148.89
4′	147.97	—	147.97
5′	111.11	1′, 3′	111.11
6′	120.76	1, 4′	120.76
3′-OMe	55.88	—	
4′-OMe	56.02	—	56.00
6-OMe	55.85	—	55.78
7-OMe	56.02	—	
COOMe	51.66	—	51.78
	51.77		
COOMe	172.66	—	172.29
	172.90		174.25

^{13}C-NMR spectrum in $CDCl_3$. The protonated carbons were assigned on the basis of a HETCOR experiment, while the ^{1}H–^{13}C connectivities were established by a long-range HETCOR measurement.

shifts and long-range coupling with the aromatic protons (H-2′, H-6′ and H-8, Table II), must be assigned to C-1 proton. Further support for these assignments in the two compounds comes from a consideration of coupling constants and the results of decoupling experiments, which require the connectivity of the C-1 protons with protons on adjacent centres as shown in Table I. Since the molecular formula requires tricyclic system and, as noted above, five aromatic protons on separate rings are present, it is clear that cyclization to an aryltetralin skeleton must have occurred. This conclusion was confirmed by HETCOR and long-range HETCOR measurements, whose results are listed in Table III.

The *trans*-relationship between H-1 and H-2 ($J_{1,2}=10$ and 9.5 Hz for AL-A and AL-B, respectively) was supported by the nuclear Overhauser effect (NOE) enhancements of the H-2′ and H-6′ signals upon irradiation of the C-2 proton (Table II). This experiment revealed a further enhancement of the H-3 signals in the spectrum of AL-A. On the other hand, irradiation of the C-1 proton in AL-A enhanced the H-2′, H-6′ and H-8 signals, as expected, and exhibited a slight effect on one of the C-4 protons, the latter being the axial proton. These results demonstrate a 1,2-*trans* and a 2,3-*cis* relationship among the substituents of the alicyclic ring in AL-A. Molecular models suggested a half chair conformation for the alicyclic ring. Conversely, DIF NOE experiments with AL-B (Table II) require a 1,2-*trans* and a 2,3-*trans* relationship among the substituents in the alicyclic ring. The stereochemical difference in the C-3 carbomethoxyl between AL-A and AL-B is also clear from the difference in chemical shifts for the ester carbonyl in the ^{13}C-NMR spectra of these compounds.

In conclusion, AL-A and AL-B were assigned the structures **2** and **3** (Chart 1), respectively. It should be noted that compound **3** has been previously reported[6] but the NMR assignments were ambiguously presented. On the other hand, compound **2** is new and has been prepared for the first time in the present study.

The mass fragmentation patterns of AL-A and AL-B can be rationalized according to Chart 2. In contrast to the aryltetralins featuring methyl or hydroxymethyl groups as substituents of the alicyclic ring,[7] the fragmentation pattern is altered by facile initial elimination of one of the carbomethoxyl groups and a hydrogen atom to afford the base peak at *m/z* 384. The latter ion undergoes further fragmentation with loss of the pendant ring C and a hydrogen atom, resulting in a stable naphthalene ring system as shown in Chart 2.

On the basis of an energy minimization calculation executed on a VAX computer using the MM2 process,[8] the conformation of AL-A showed a minimal energy *ca.*

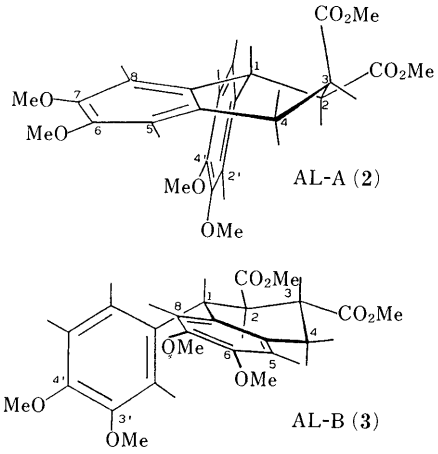


Fig. 1. Representations of the Conformations of **2** and **3**, Derived by Use of the MM2 Program

TABLE IV. Calculated Dihedral Angles for Alicyclic Protons of **2** and **3**

θ	AL-A (**2**)	AL-B (**3**)
1,2	169°	163°
2,3	49°	166°
3,4ax	44°	163°
3,4eq	72°	61°

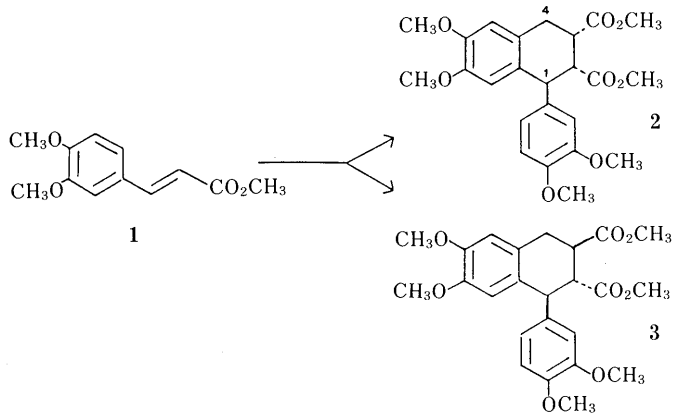


Chart 1

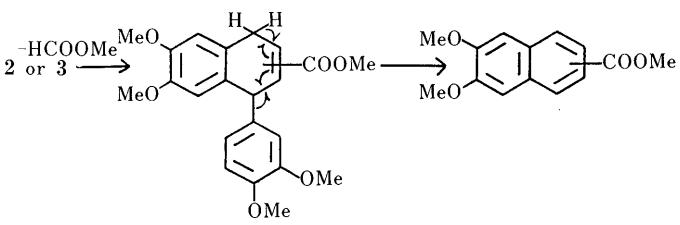


Chart 2

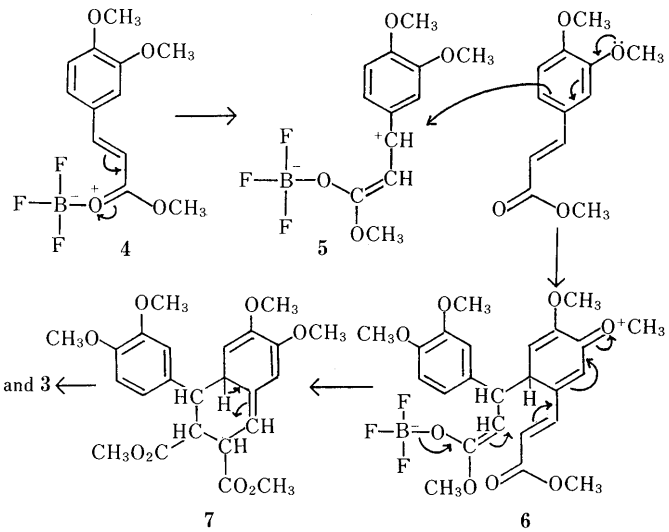


Chart 3

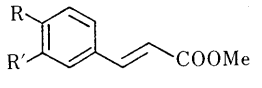
0.8 kcal/mol lower than that of AL-B. These results (Fig. 1) are in good agreement with the proposed structures and explain the different yields of AL-A and AL-B. The calculated dihedral angles (Table IV) of the minimal energy conformers of AL-A and AL-B are also in good agreement with the experimental coupling constants.

The non-oxidative coupling of methyl-(*E*)-3,4-dimethoxycinnamate to afford **2** and **3** can be rationalized according to the mechanism shown in Chart 3. Thus, initial activation of the unsaturated carbonyl system can be achieved through coordination with BF_3, as shown, to afford the resonance-stabilized carbocation **4** and/or **5**, which then undergoes facile attack by a second molecule of the starting material. The resulting intermediate **6** undergoes further cyclization and aromatization to afford the isolated products. It is clear from this postulate that the attack on the carbocation **5** requires an electron-rich aromatic system so as to achieve the carbon–carbon bond formation shown in **6**. Furthermore, this reaction involving nucleophilic attack should be independent of light since radical species are not involved. For this reason, additional experiments concerning the influence, if any, of light and the effect of substituents on the aromatic ring were performed.

First of all, the above reaction was repeated under the above-noted conditions but in the absence of light. The yield of AL-A and AL-B (90%) clearly revealed that light activation is not required, and Lewis acid catalysis by BF_3 as proposed in Chart 3 remains reasonable.

The next study considered the influence of substituents in the aromatic rings of the substrate on the yields of "coupling" products similar in structure to **2** and **3**. For this purpose, the cinnamic ester analogues shown in Chart 4 were studied.

The *para*- and *meta*-nitro substituted compounds **10** and **11** and the *meta*-methoxy isomer **9** were recovered unchanged. On the other hand, the *para*-methoxy isomer **8** reacted to afford a number of unidentified products. However, when a 1 : 1 mixture of **8** and **9** was reacted under the above conditions, an interesting result was obtained: **8** had totally reacted and a number of unidentified products were formed, but only 50% of **9** was recovered and a new product (in 50% yield, based on **8** consumed) could be isolated and characterized. The spectral data (see Experimental) supported the structure **14**, clearly formed from the coupling of one unit of **8** with one unit of **9**. Chart 5 provides a *rationale* for the formation of **14** (the numbering is arbitrary).



	R	R′
8	OMe	H
9	H	OMe
10	NO_2	H
11	H	NO_2

Chart 4

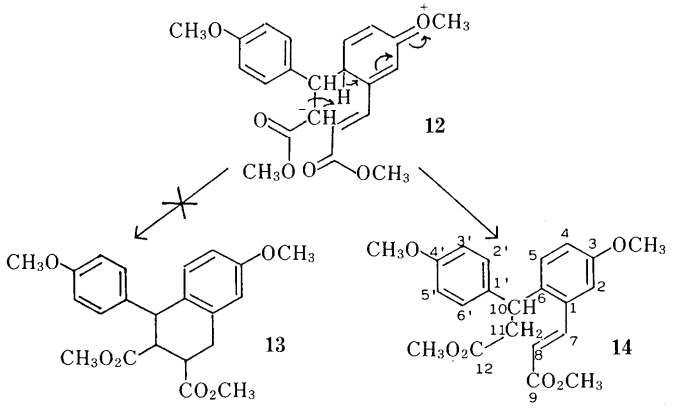


Chart 5

The coupling of **8** and **9** requires the initial formation of a carbocation derived from **8**, in a manner similar to that depicted for compound **1** (Chart 3). The subsequent step of the mechanism involves a protonation of intermediate **12** to afford **14** and not the intramolecular cyclization of the carbanionic species to the conjugated ester moiety as required in the formation of **13**. It is therefore obvious that the additional methoxyl function in intermediate **6** (Chart 3) affords a longer "lifetime" for intramolecular attack to provide **2** and **3** and this process takes preference over the alternative protonation, as proposed for the formation of **14**. The reason for this variation in reaction mechanism is not entirely clear but perhaps it relates to additional stabilization through orbital overlap of the π-system in the intermediate **6** with the electron pair of the 4-methoxyl group, a factor which is lacking in **14**.

It is clear that strongly electron-withdrawing groups such as the nitro group completely inhibit the reaction, as expected. In the latter cases, the formation of the cation corresponding to **5** is energetically unfavorable and, even if it is formed, the subsequent carbon–carbon bond-forming process to afford the intermediate corresponding to **6** is also retarded.

To examine further the generality of this reaction, (*E*)-3,4-methylenedioxycinnamic acid methyl ester (**15**) was studied. The results are similar to those noted above for the 3,4-dimethoxy series, and compounds **16** and **17** (Chart 6) were isolated and characterized.

On the other hand, the 3,4,5-trimethoxycinnamate ester afforded a complex mixture and the above reaction does not provide a convenient route to the corresponding aryltetralins in this series.

Finally, it should be noted that (*E*)-2,4-dimethoxycinnamic acid methyl ester provides completely different products, the study of which will be presented in another publication.

In summary, the BF_3-catalyzed reaction of 3,4-di-

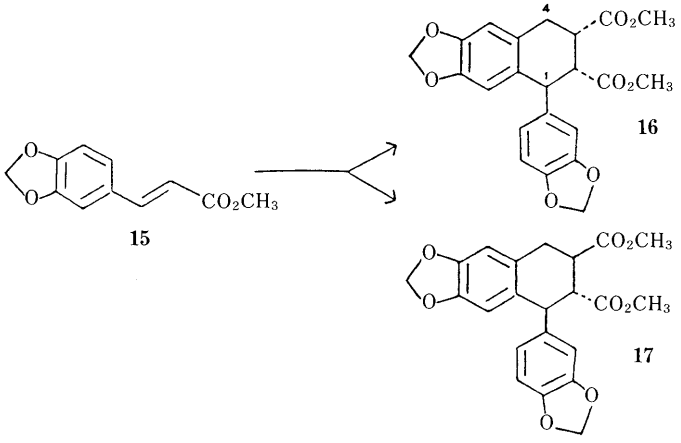


Chart 6

oxygenated cinnamic acid esters does afford an excellent route to the corresponding aryltetralins. The substituents must be electron-donating. Other substitution patterns, that is 2,4- or 3,4,5-functionalized systems, cannot successfully be employed for synthesis of the corresponding aryltetralins.

Experimental

All melting points were determined on a Kofler apparatus and are uncorrected. The UV spectra were recorded with a Perkin-Elmer Lambda 5 spectrophotometer. The MS and high resolution (HR) MS were measured with a VG 70/70 EQ-HS instrument. The ^{1}H- and ^{13}C-NMR spectra were obtained with a Varian XL-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometer. Chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane as an internal standard, and coupling constants are in hertz (Hz). Column chromatography was carried out on silica gel (Kieselgel 60, Merck). Thin-layer chromatography (TLC) was performed on silica gel (Kieselgel 60 F_{254}, Merck).

Dimethyl *trans*(1,2),*cis*(2,3)-6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-1,-2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (AL-A, 2) $BF_3 \cdot Et_2O$ (0.1 ml) was added to a solution of (*E*)-3,4-dimethoxycinnamic acid methyl ester (**1**, 100 mg) in CH_2Cl_2 (5 ml), and the mixture was stirred at room temperature for 24 h. Evaporation of the solution and silica gel column chromatography of the resulting residue (hexane–EtOAc, 85 : 15) afforded **1** (8 mg), **2** (54 mg), **3** (19 mg) and a mixture of **2** and **3** (18 mg). Total yield 90%. mp 141—142 °C (MeOH). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 241 (4.08), 287 (3.94). ^{1}H-NMR: see Table I. ^{13}C-NMR: see Table III. EI-MS *m/z* (%): 444 (56) M^+, 384 (100) M−HCOOMe, 371 (15) $M-C_3H_5O_2$, 370 (16), 325 (26), 384−COOMe, 311 (26) 371−AcOH, 246 (11) 384−ring C. HRMS Calcd for $C_{24}H_{28}O_8$ *m/z* 444.1784. Found *m/z* 444.1775.

Dimethyl *trans*(1,2),*trans*(2,3)-6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (AL-B, 3) mp 125—126 °C (MeOH, lit.[6] mp 127 °C). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 241 (4.12), 286 (3.95). ^{1}H-NMR: see Table I. ^{13}C-NMR: see Table III. EI-MS *m/z* (%): 444 (63) M^+, 384 (100) M−HCOOMe, 371 (29) $M-C_3H_5O_2$, 370 (32), 325 (43) 384−COOMe, 311 (48) 371−AcOH, 246 (11) 384−ring C.

Methyl (*E*)-5-Methoxy-2-[2-methoxycarbonyl-1-(4-methoxyphenyl)-ethyl]-2-carboxylate (14) A mixture of **8** (50 mg) and **9** (50 mg) was reacted under the same conditions as used for **1**. Evaporation of the solution and silica gel column chromatography of the resulting residue (CH_2Cl_2–EtOAc, 95 : 5) afforded **9** (22 mg) and **14** (24 mg). Oil. UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 242 (4.44), 277 (4.43), 324 (3.89). ^{1}H-NMR ($CDCl_3$) δ: 8.13 (1H, d, J=15.5 Hz, H-7), 7.20 (1H, d, J=8.7 Hz, H-5), 7.08 (2H, d, J=8.7 Hz, H-2′, H-6′), 7.01 (1H, d, J=2.7 Hz, H-2), 6.91 (1H, dd, J=8.7, 2.7 Hz, H-4), 6.79 (2H, d, J=8.7 Hz, H-3′, H-5′), 6.25 (1H, d, J=15.5 Hz, H-8), 4.82 (1H, t, J=7 Hz, H-10), 3.78 (6H, s, 3-OMe, 4′-OMe), 3.75 (3H, s, 8-COOMe), 3.58 (3H, s, 11-COOMe), 3.00 (2H, d, J=7 Hz). APT ^{13}C-NMR δ: 171.93 (C-12), 167.02 (C-9), 158.09 (C-3, C-4′), 142.45 (C-8), 135.17, 134.89, 134.47 (C-1, C-6, C-1′), 128.52 (C-2′, C-6′), 128.12 (C-5), 120.17 (C-7), 115.89 (C-2), 113.95 (C-3′, C-5′), 112.07 (C-4), 55.23, 55.12 (2×OMe), 51.66 (2×COOMe), 41.21 (C-10), 40.96 (C-11). EI-MS *m/z* (%): 384 (22) M^+, 352 (25) M−MeOH, 324 (38) M−HCOOMe, 311 (100) $M-CH_2COOMe$, 279 (40) 311−MeOH, 265 (24), 251 (88) 311−HCOOMe, 237 (13), 191 (15).

Dimethyl *trans*(1,2),*cis*(2,3)-6,7-Methylenedioxy-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (16) BF_3Et_2O (0.1 ml) was added to a solution of (*E*)-3,4-methylenedioxycinnamic acid methyl ester (**15**, 100 mg) in CH_2Cl_2 (5 ml), and the mixture was stirred at room temperature for 24 h. Evaporation of the solution and silica gel column chromatography of the resulting residue ($CHCl_3$) gave **15** (11 mg), **16** (61 mg) and **17** (25 mg). Total yield 86%. mp 150—151 °C (MeOH). UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 242 (4.15), 291 (4.17). ^{1}H-NMR ($CDCl_3$) δ: 6.74 (1H, d, J=8 Hz, H-5′), 6.70 (1H, dd, J=2, 8 Hz, H-6′), 6.69 (1H, br s, H-5), 6.64 (1H, d, J=2 Hz, H-2′), 6.34 (1H, br s, H-8), 5.94 (2H, s, OCH_2O), 5.93, 5.91 (1H each, d, J=1.5 Hz, OCH_2O), 4.60 (1H, d, J=10 Hz, H-1), 3.93 (1H, dt, J=7, 8 Hz, H-3), 3.69, 3.64 (3H each, s, 2×COOMe), 3.43 (1H, dd, J=8, 10 Hz, H-2), 2.60 (1H, dd, J=15, 7 Hz, H-4eq), 2.44 (1H, dd, J=15, 8 Hz, H-4ax). APT ^{13}C-NMR ($CDCl_3$) δ: 172.67, 172.42 (2×COOMe), 147.86, 147.66, 147.25, 146.62 (C-6, C-7, C-3′, C-4′), 137.36 (C-1′), 136.63 (C-10), 136.16 (C-9), 121.92 (C-6′), 108.51 (C-5′), 108.26 (C-2′), 105.64 (C-8), 104.48 (C-5), 101.20, 100.98 (2×OCH_2O), 58.55 (C-2), 51.79, 51.69 (2×COOMe), 51.30 (C-1), 42.14 (C-3), 36.70 (C-4). EI-MS *m/z* (%): 412 (31) M^+, 352 (100) M−HCOOMe, 339 (56) $M-C_3H_5O_2$, 338 (60), 293 (34) 352−COOMe, 279 (45) 338−COOMe, 230 (23) 352−ring C: m* 300.7 (412→352), 243.9 (352→293). HRMS Calcd for $C_{22}H_{20}O_8$ *m/z* 412.1158. Found *m/z* 412.1147.

Dimethyl *trans*(1,2),*trans*(2,3)-6,7-Methylenedioxy-1-(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (17) Vitreous solid. UV $\lambda_{max}^{CHCl_3}$ nm (log ε): 241 (4.07), 291 (4.09). ^{1}H-NMR ($CDCl_3$) δ: 6.75 (1H, d, J=8 Hz, H-5), 6.69 (1H, dd, J=2, 8 Hz, H-6′), 6.65 (1H, d, J=2 Hz), 6.63 (1H, d, J=1 Hz, H-5), 6.32 (1H, d, J=1 Hz, H-8), 5.95, 5.94 (1H each, d, J=1 Hz, OCH_2O), 5.93, 5.91 (1H, each, d, J=1.5 Hz, OCH_2O), 4.46 (1H, d, J=9.5 Hz, H-1), 3.79 (ddd, J=6, 7, 9.5 Hz, H-3), 3.70, 3.69 (3H each, s, 2×COOMe), 3.03 (1H, t, J=9.5 Hz, H-2), 2.87 (1H, dd, J=16, 6 Hz, H-4eq), 2.73 (1H, dd, J=16, 7 Hz, H-4ax). APT ^{13}C-NMR ($CDCl_3$) δ: 174.12 (3-COOMe), 172.32 (2-COOMe), 147.95, 147.59, 147.52, 146.65 (C-6, C-7, C-3′, C-4′), 137.30 (C-1′), 136.89 (C-10), 136.02 (C-9), 121.83 (C-6′), 108.48 (C-5′), 108.26 (C-2′), 105.39 (C-8), 103.48 (C-5), 101.27, 101.03 (2×OCH_2O), 61.10 (C-2), 53.52 (C-1), 51.94, 51.73 (2×COOMe), 43.68 (C-3), 38.77 (C-4). EI-MS *m/z* (%): 412 (29) M^+, 352 (100) M−HCOOMe, 339 (47) $M-C_3H_5O_2$, 338 (52), 293 (35), 352−COOMe, 279 (52) 338−COOMe, 230 (18) 352−ring C. HRMS Calcd for $C_{22}H_{20}O_8$ *m/z* 412.1158. Found *m/z* 412.1142.

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