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A Short Asymmetric Synthesis of (+)-Lyoniresinol Dimethyl Ether

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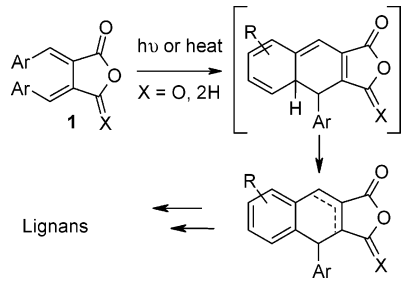
A short, efficient synthesis of the lignan (+)-lyoniresinol dimethyl ether is described. The synthesis is achieved by asymmetric photocyclization of an achiral dibenzylidenesuccinate to a chiral aryldihydronaphthalene. (−)-Ephedrine is used as a chiral auxiliary to bias the atropisomeric equilibrium in the dibenzylidenesuccinate prior to the photochemical reaction. The synthesis of the title compound was accomplished in five steps, and the final product was recrystallized to constant melting point and rotation.

Introduction

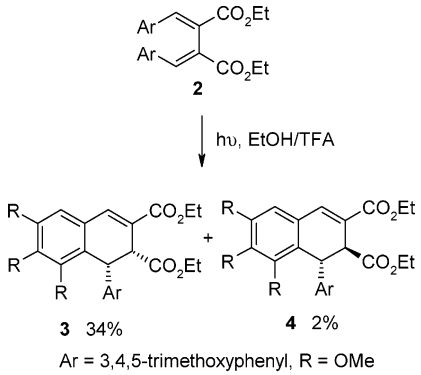
There are several papers in the literature on the use of 2,3-dibenzylidenesuccinate derivatives, particularly fulgides (the cyclic anhydrides of (*E*,*E*)-dibenzylidenesuccinic acids, **1**, X = O) and the corresponding lactones (**1**, X = 2H), as starting materials for the synthesis of arylnaphthalene lignans (including dihydro and tetrahydro derivatives) (Scheme 1).[1−11] The syntheses involve cyclization of the 2,3-dibenzylidenesuccinate derivative to an unstable 1,8a-dihydronaphthalene (1,8a-DHN) followed by isomerization to a 1,2- or 1,4-DHN from which lignans can easily be prepared.

Although an interesting methodology, there are no examples yet of its use for the synthesis of optically active lignans (asymmetric synthesis). In this paper, we describe a method for photochemically converting a 2,3-dibenzylidenesuccinate precursor to an optically active dihyronaphthalene (DHN) and subsequent transformation of the DHN into the optically pure lignan (+)-lyoniresinol dimethyl ether.

SCHEME 1. Photochemistry of 2,3-Dibenzylidenesuccinates



SCHEME 2. Photocyclization of (*E*,*E*)-2,3-Di(3,4,5-trimethoxybenzylidene)Succinate, 2



Results and Discussion

We previously observed that simple diesters of (*E*,*E*)-2,3-dibenzylidenesuccinates such as diethyl (*E*,*E*)-2,3-di-(3,4,5-trimethoxybenzylidene)succinate (**2**) in ethanol could be photochemically converted in modest yield to the *cis*-1,2-dihydronaphthalene (*cis*-1,2-DHN, **3**), accompanied by smaller amounts of *trans*-1,2-DHN (**4**) (Scheme 2).[11]

It was also noted that the methylene protons of the ethyl groups of the 2,3-dibenzylidenesuccinate **2** appeared

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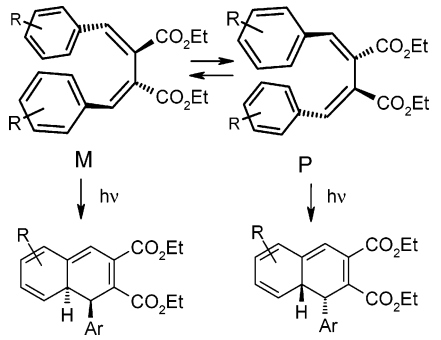
SCHEME 3. Atropisomeric Forms of Dibenzylidenesuccinates



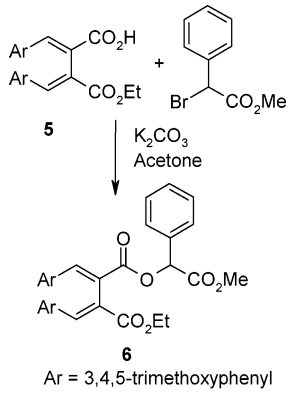
to be nonidentical (diastereotopic) in the NMR spectrum. It was concluded, as had been noted previously,[12−14] that 2,3-dibenzylidenesuccinates, such as **2**, have a barrier to rotation about the central single bond and that they exist at room temperature as an equilibrium mixture of the two enatiomeric atropisomers (Scheme 3).

The fact that (*E*,*E*)-2,3-dibenzylidenesuccinates exist as enantiomeric atropisomers suggested that their photocyclization might be stereoselective (pericyclic conrotatory cyclization) with the *M* conformation giving the (1*R*)-1,8a-dihydronaphthalene and the *P* conformation giving the (1*S*)-1,8a-dihydronaphthalene (Scheme 3). The designation of the atropisomers of **2** as *P* or *M* is based on the standard nomenclature for axially chiral molecules where the point of view in this case is parallel to the central single bond of the butadiene.[15] The subsequent rearrangement of the 1,8a-dihydronaphthalenes to either 1,2- or 1,4-DNPs should not affect the configuration at the 1-center, and thus, the overall reaction of either the *M* or *P* form of the 2,3-dibenzylidenesuccinate would provide an asymmetric synthesis of a lignan precursor. What remained was to find a way to bias the 2,3-dibenzylidenesuccinate **2** to adopt only one of its two axially chiral forms.

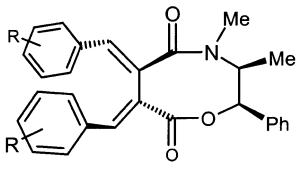
With the idea that a chiral ester corresponding to **2** might adopt a single atropisomeric form, the mandelate ester **6** was prepared as shown (Scheme 4). The monoacid **5** was prepared using a previously described method.[11] Reaction of the crude **5** with methyl α-bromophenylacetate in the presence of potassium carbonate gave chiral ester **6**. The NMR spectrum of **6** in $CDCl_3$ clearly indicated that it was an approximately 50:50 mixture of two diasteriomers, presumably rotamers about the central bond of the diene. The two spectra collapsed to a single average spectrum when the spectrum was acquired in DMSO at 80 °C.

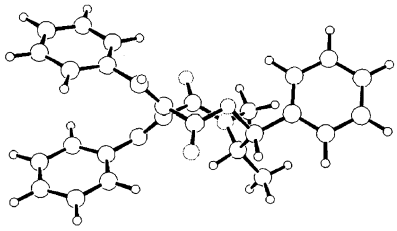
Since the acyclic mandelate ester **6** was not at all prejudiced to adopt a single rotameric form, attempts were made to prepare cyclic chiral esters or amide esters. We were unable to prepare the diethyl tartrate cyclic diester but were eventually successful in preparing the (−)-ephedrine cyclic amide ester **7** (Scheme 5). The NMR spectrum of **7** showed no evidence for the presence of two

SCHEME 4. Preparation of Mandelyl Ester 6



SCHEME 5. Cyclic Amide Ester 7





equilibrating diastereomers, and it was concluded that it existed as a single rotameric form.

It was tentatively concluded that the preferred conformation of **7** was the *M* form shown in Scheme 5 as this was the lowest energy conformation that could be found using the Spartan molecular mechanics program (computations were made on the nonmethoxylated compound to save computing resources). The very large rotation of **7** (−343°), a value too large to be accounted for by the ephedrine chiral auxiliary alone, also suggested that **7** was in an extreme conformation. (−)-Hexahelicene, which has the same left-handed helical configuration as shown for **7** in Scheme 5**,** also has a very large negative rotation.[16]

Irradiation of **7** at 254 nm in 2-propanol followed by crystallization of the major product from the irradiation solution gave a 26% isolated yield of a product whose structure was tentatively assigned to that shown as structure **8** (Scheme 6). Interestingly, compound **8** had a rotation of +476°, a very large optical rotation opposite to that of **7**.

An NMR spectrum of the evaporated crude product mixture before crystallization of **8** indicated that the major compound, **8**, made up approximately 60% of the product mixture along with 40% of a second compound. This second compound was isolated by column chroma-

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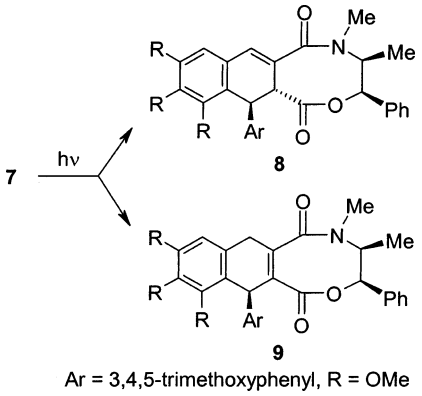
SCHEME 6. Irradiation of 7



tography of the mother liquors and was identified as the 1,4-dihydro isomer **9** (Scheme 6). Although the absolute stereochemistry of **9** was not determined, it was presumed to be the same as in **8**.

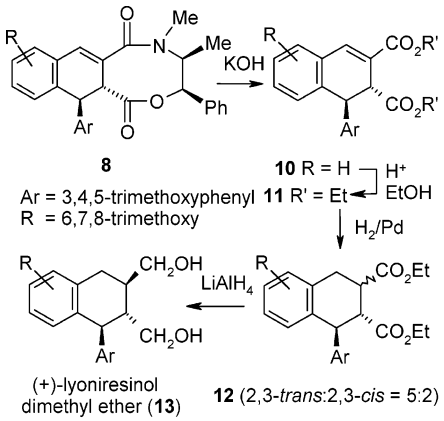
The gross structure of **8** was assigned by NMR spectroscopy. There was little or no coupling between the allylic proton at 4.22 ppm and the benzylic proton at 4.84 ppm consistent with a 1,2-trans relative configuration (either 1*R*,2*S* or 1*S*,2*R*). A similarly small coupling constant was observed in **4**.[11] It is notable that the irradiation of the acyclic diethyl ester **2** gave the cis isomer **3** as a major product and the trans isomer **4** as a minor product in contrast to the irradiation of **7**, which gave the trans isomer as the major product. If **7** initially cyclizes directly to a 1,8a-DHN then its subsequent rearrangement to *trans*-**8** must involve solvent protonation as a concerted 1,5-sigmatropic shift of hydrogen (from position 8 to position 2) would be impossible. This observation is consistent with earlier work by Heller who had tentatively concluded that rearrangements of this type do not involve a concerted sigmatropic shift.[17] On the other hand, if the double bond adjacent to the ester group in **7** were to photoisomerize to the trans configuration, a subsequent photocylization could then be followed by an allowed, and sterically possible, 1,5-sigmatropic shift to give the observed trans product **8**. No experiments were conducted to resolve this ambiguity although the former seems more likely based on Heller's earlier work.

The regioselectivity of the photochemical closure of **7** to form **8** was confirmed by NMR spectroscopy using heteronuclear multiple-bond correlation (HMBC) spectroscopy. The cyclization had occurred to the aryl ring adjacent to the amide functionality.

The absolute stereochemistries at carbon centers 1 and 2 were still unconfirmed and could only be determined absolutely by conversion to a compound whose configurations at those two centers were known.

Removal of the chiral auxiliary from compound **8** was easily accomplished by refluxing in 3 M KOH in methanol (Scheme 7). The resulting diacid **10** was re-esterified to the diethyl ester **11** that had been reported earlier in its racemic form.[11,18]

SCHEME 7. Final Steps in the Synthesis of (+)-Lyoniresinol Dimethyl Ether



Reduction of **11** with hydrogen (Pd/C) gave the saturated diester **12**. Contrary to previous reductions of this type that had given almost exclusively the all-trans product,[11] **12** was formed as a 5:2 mixture of the 2,3-trans/2,3-cis compounds. Attempts to improve the stereoselectivity by changing the solvent (ethanol and methanol), temperature (rt and reflux), and catalyst (Pd/C and Ru/C) proved fruitless.

Reduction of **12** (mixture of stereoisomers) with $LiAlH_4$ gave (+)-lyoniresinol dimethyl ether as a major product and its 2,3-cis diastereomer as a minor product. Repeated crystallization (three times) from methylene chloride/hexanes produced the pure (+)-lyoniresinol dimethyl ether of constant melting point 157−159 °C and rotation $[\alpha]^{25}_D = +41.2$ (*c* 0.7, $CHCl_3$). The melting point was consistent with that reported previously (158−160 °C),[19] and the NMR spectrum was consistent with previously published data.[20,21] The rotation was different from, but not inconsistent with, earlier reports of +49.4 for the originally isolated material[22] and later reports of +21.5,[23] +26.0,[24] and +30.0[24] (the concentrations and solvents used for these determinations were not all the same).

The important aspect of the rotation of the finally synthesized material was that the sign of the rotation was positive, confirming the assignment of the 1*S*,2*R* configuration for compounds **8**, **10**, **11**, and **12**. This also means that the photocyclization of **7** did occur by a conrotatory closure from the *M* conformation of **7** as had been predicted.

The synthesis of (+)-lyoniresinol was thus accomplished by the rather unique method of constraining precursor (**7**) to adopt a single atropisomeric and chiral form and using that atropisomeric form to synthesize an optically active natural product.

Experimental Section

Ethyl Methylmandelyl (*E*,*E*)-Dibenzylidenesuccinate (6). Methyl α-bromophenylacetate (0.29 mL, 1.84 mmol) was added to a stirred solution of bis(3,4,5-trimethoxybenzylidene)-

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succinate monoacid ester **5**[11] (0.841 g, 1.67 mmol) and K_2CO_3 (1.17 g, 8.46 mmol) in acetone (10 mL), and the solution was stirred at reflux for 14 h. The reaction mixture was filtered, the precipitate washed with acetone, and the filtrate evaporated. The residue was dissolved in CH_2Cl_2, dried over anhydrous magnesium sulfate, and stripped of solvent under reduced pressure to give an orange oil as crude product (0.986 g, 91%). The diester was purified by flash column chromatography on silica gel (50 mL) using 30% EtOAc/hexanes as the eluent to afford a cream-colored amorphous solid (0.367 g, 34%): ^{1}H NMR ($CDCl_3$) (a mixture of diasteromers) δ 1.00 (t, 3H, J = 7.1), 1.11 (t, 3H, J = 7.1), 3.59 (s, 3H), 3.63 (s, 3H), 3.69 (s, 6H), 3.71 (s, 6H), 3.74 (s, 12H), 3.81 (s, 12H), 4.07 (m, 2H), 4.17 (m, 2H), 5.91 (s, 1H), 5.98 (s, 1H), 6.68 (s, 2H), 6.73 (s, 2H), 6.76 (s, 2H), 6.79 (s, 2H), 7.32 (m, 10H), 7.83 (s, 1H), 7.87 (s, 1H), 7.88 (s, 1H), 7.89 (s, 1H); ^{13}C NMR ($CDCl_3$) (a mixture of two diastereomers) δ 14.0 (CH_3), 14.1 (CH_3), 52.5 (CH_3), 55.9 (CH_3), 56.0 (CH_3), 56.1 (CH_3), 60.8 (CH_3), 60.9 (CH_3), 61.2 (CH_2), 61.3 (CH_2), 75.0 (2 × CH), 107.0 (CH), 107.3 (CH), 125.8 (C), 126.2 (2 × C), 127.4 (2 × CH), 128.7 (2 × CH), 129.1 (2 × CH), 129.9 (C), 130.0 (C), 130.1 (C), 133.8 (C), 139.4 (C), 139.5 (C), 139.7 (C), 139.8 (C), 142.8 (CH), 143.2 (CH), 143.5 (CH), 153.1 (2 × CH), 166.1 (C), 166.2 (C), 166.7 (C), 168.9 (C); mass spectrum *m*/*z* (relative intensity) 650 (M^+, 11), 501 (21), 411 (37), 195 (100), 181 (72), 91 (52), 77 (18); HRMS calcd for $C_{35}H_{38}O_{12}$ 650.2363, found 650.2356.

(*E*,*E*)-2,3-Di(3,4,5-trimethoxxybenzylidene)succinate (−)-Ephedrine Cyclic Amide Ester (7). To a solution of (*E*,*E*)-2,3-di(3,4,5-trimethoxybenzylidene)succinic acid[25] (0.5 g, 1.05 mmol) in CH_2Cl_2/DMF (45 mL, 3:1) cooled to 0 °C were added TBTU (0.337 g, 1.05 mmol) and DIEA (0.55 mL, 3.16 mmol). The solution was allowed to stir under nitrogen at 0 °C for 30 min. A second solution of (1*R*,2*S*)-(−)-ephedrine (0.174 g, 1.05 mmol) in CH_2Cl_2/DMF (25 mL, 3:1) was added slowly and dropwise over 30 min. The resulting mixture was stirred under nitrogen at 0 °C for 1 h 30 min and then at room temperature overnight. After the mixture was cooled to 0 °C, a further equivalent of TBTU (0.337 g, 1.05 mmol) was added and the reaction stirred under nitrogen at 0 °C for 1 h 30 min and for an additional 18 h at room temperature. CH_2Cl_2 was evaporated, and the residue was mixed with water (50 mL) and acidified with 10% aqueous HCl (25 mL). The crude reaction product was extracted with EtOAc. The combined organic layers were washed with brine and dried over magnesium sulfate, filtered, and evaporated to dryness to give a brown oil. The crude product was purified by flash column chromatography (EtOAc/hexanes, 60:40) to afford an orange oil that solidified (0.277 g, 0.46 mmol) in 44% yield: $[\alpha]^{25}_D$ = −342.9 (c = 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3H, J = 7.0 Hz), 2.90 (s, 3H), 3.81 (s, 3H), 3.82 (s, 6H), 3.86−3.88 (m, 4H), 3.90 (s, 6H) 6.29 (s, 1H), 6.79 (s, 2H) 7.07 (s, 2H) 7.30 (s, 1H) 7.32−7.43 (m, 5H); 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.8, 35.8, 56.1 (2), 56.4 (2), 60.81, 60.84, 64.6, 81.2, 107.3 (2), 108.4 (2), 125.7 (2), 126.1, 128.4, 128.67, 128.74, 129.0, 129.5, 139.4, 139.7, 139.9, 146.3, 145.4, 153.1 (2), 153.2 (2), 168.0, 169.9; MS-EI *m*/*z* (relative intensity) 603 (M^+ 20), 557 (25), 500 (12), 454 (33), 411 (20), 392 (16), 289 (11), 245 (8), 181 (32), 168 (54), 146 (24), 56 (100); HRMS for $C_{34}H_{37}NO_9$ calc 603.2458, found 603.2468.

(1*S*,2*R*)-1-(3,4,5-Trimethoxyphenyl)-6,7,8-trimethoxy-1,2-dihydronaphthalene-2,3-dicarboxylate (−)-Ephedrine Cyclic Amide Ester (8) and (1*S*,2*R*)-1-(3,4,5-Trimethoxyphenyl)-6,7,8-trimethoxy-1,4-dihydronaphthalene-2,3-dicarboxylate (−)-Ephedrine Cyclic Amide Ester (9). Compound **7** (0.7712 g, 1.28 mmol) was dissolved in 2-propanol (700 mL), 100 mL aliquots of that solution were placed in a Vycor cylinder and purged with nitrogen for 15 min, and the solution was irradiated for 30 min (254 nm). NMR spectroscopy of a small aliquot that was evaporated to dryness showed the presence of two compounds in an approximately 6:4 ratio. The combined irradiated solutions were concentrated and cooled to 0 °C overnight. The precipitate was filtered to give colorless crystals of the major product (202.4 mg, 0.34 mmol, 26%): $[\alpha]^{25}_D$ = +475.7 (c = 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3H, J = 7.0 Hz) 2.50 (s, 3H) 3.77 (s, 3H) 3.80 (s, 3H) 3.84 (s, 6H) 3.86 (s, 3H) 3.88 (s, 3H), 4.22 (s, 1H), 4.38−4.48 (m,1H), 4.84 (s, 1H), 5.37 (d, 1H, J = 4.0 Hz), 6.48 (s, 1H), 6.50 (s,1H), 6.69 (s, 2H), 7.28−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.4, 29.4, 36.8, 52.3, 55.6, 56.0, 56.1 (2C), 60.7, 60.8 (2C) 78.8, 104.3 (2C), 107.4, 121.6, 124.8, 127.5 (2C), 127.6, 128.2 (2C), 128.7, 128.8, 133.6, 136.9, 140.1, 143.5, 151.4, 152.5, 153.2 (2C), 172.5, 172.7; MS-EI *m*/*z* (relative intensity) 603 (M^+ 35), 557 (14), 502 (12), 454 (13), 441 (11), 412 (28), 369 (14), 245 (11), 181 (15), 168 (16), 105 (27), 56 (100); HRMS for $C_{34}H_{37}NO_9$ calcd 603.2468, found 603.2475.

In a similar experiment carried out on a smaller amount of **7** (100 mg) the mother liquors recovered after crystallization of **8** were evaporated and chromatographed (ethyl acetate/hexanes) to give 16 mg (16%) of the minor compound **9** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 2H, J = 7.0 Hz), 2.48 (s, 3H), 3.54 (dd, 1H, J = 1.1, 22.2 Hz), 3.67 (s, 3H), 3.78 (s, 6H), 3.79 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.15 (dq, 1H, J = 7.0, 3.7 Hz), 4.41 (dd, 1H, J = 3.2, 22.2 Hz), 5.35 (d, 1H, J = 3.7 Hz), 5.72 (dd, 1H, J = 1.1, 3.2 Hz), 6.48 (s, 2H), 6.54 (s, 1H), 7.28 (m. 2H), 7.35 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 13.9, 29.8, 36.9, 40.8, 55.3, 56.1_7, 56.2_2 (2C), 60.8, 60.9 (2C), 85.8, 105.4 (2C), 105.9, 123.7, 127.3 (2C), 128.4 (2C), 128.5, 128.8, 134.2, 134.7, 137.1, 138.4, 141.4, 145.3, 151.0, 153.0, 152.3 (2C), 169.8, 172.1; MS-EI *m*/*z* (relative intensity) 603 (M^+ 75), 441 (47), 436 (100), 425 (39), 412 (58), 381 (47), 329 (58), 289 (36), 195 (49), 181 (36), 168 (64), 148 (47), 147 (45), 91 (34); HRMS for $C_{34}H_{37}NO_9$ calcd 603.2468, found 603.2455.

(1*S*,2*R*)-1-(3,4,5-Trimethoxyphenyl)-6,7,8-trimethoxy-1,2-dihydronaphthalene-2,3-dicarboxylic Acid (10). To compound **8** (202.4 mg, 0.34 mmol) was added a methanolic solution of 3 M KOH (50 mL). The mixture was refluxed under nitrogen for 3 h and the methanol then partially evaporated. The solution was acidified with 10% aqueous HCl (150 mL) and extracted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness to give a colorless oil that solidified (0.1832 g). The crude compound was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3H), 3.70 (s, 6H), 3.76 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.02 (s, 1H), 5.02 (s, 1H), 6.22 (s, 2H), 6.73 (s, 1H), 7.73 (s, 1H).

Diethyl (1*S*,2*R*)-1-(3,4,5-Trimethoxyphenyl)-6,7,8-trimethoxy-1,2-dihydronaphthalene-2,3-dicarboxylate (11). To crude **7** (183.2 mg, 0.39 mmol) was added anhydrous EtOH (50 mL) followed by H_2SO_4 (concd, 1.5 mL) and the solution refluxed under nitrogen overnight. The ethanol was evaporated and the residue diluted with water and extracted with EtOAc. Flash column chromatography of the ethyl acetate extract (silica gel, EtOAc/hexanes, 60:40) gave **11** as a colorless oil that solidified (111.4 mg, 0.21 mmol, 54%). This product was spectroscopically identical to the racemic compound previously reported,[18] but with rotation $[\alpha]^{25}_D$ = +129.7 (c = 0.9, MeOH).

Diethyl (1*S*,2*R*)-1-(3,4,5-Trimethoxyphenyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalene-2,3-dicarboxylate (12). Diester **11** (111.4 mg, 0.21 mmol) was added to nitrogen-purged methanol (30 mL), 5% Pd/C (60 mg) was added, and the solution was vigorously stirred under H_2 atmosphere at room temperature overnight. The Pd/C was filtered off using Celite. The methanol was evaporated to dryness to give a colorless oil that solidified (97.7 mg, 0.18 mmol, 87%). The diastereomeric ratio (78:22) was determined by ^{1}H NMR of the crude product (δ 6.25 for major isomer, δ 6.22 for minor isomer). The product was used in the next step with no further purification.

(+)-Lyoniresinol Dimethyl Ether (13). Dry THF (40 mL) was introduced into a nitrogen-purged 100 mL round-bottom flask containing the isomeric mixture of **12** (97.7 mg, 0.18

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mmol) and $LiAlH_4$ (80 mg, 2.11 mmol). The resulting slurry was stirred at room temperature for 3 h. Workup was achieved using Fieser's method: consecutive slow adjunction of water (0.24 mL), 15% aqueous NaOH (0.24 mL), and water (0.72 mL). The granular precipitate was filtered off using Celite. The filtrate was evaporated to dryness to give a colorless oil residue that solidified (89.6 mg, 0.20 mmol). The diastereomeric ratio (80:20) was determined by ^{1}H NMR spectroscopy of the crude product (δ 6.33 for major isomer, δ 6.19 for minor isomer). Three recrystallizations from CH_2Cl_2/hexanes of the crude product gave the major isomer as the pure diastereoisomer **12**: mp 157−159 °C; $[\alpha]^{25}_D = +41.2$ (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.72−1.94 (m, 2H), 2.58−2.77 (m, 2H), 3.22 (s, 3H), 3.59−3.87 (m, 4H), 3.75 (s, 3H), 3.77 (s, 6H), 3.79 (s, 3H), 3.85 (s, 3H), 3.97 (d, 1H, $J = 8.0$ Hz), 6.30 (s, 2H), 6.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0, 40.2, 43.7, 49.4, 55.8, 56.2, 59.6, 60.5, 60.9, 63.7, 66.6, 105.8, 106.7, 125.0, 133.1, 136.2, 140.7, 143.3, 152.0, 152.1, 152.9; EI-MS *m*/*z* (relative intensity) 448 (M^+ 38), 430 (100), 399 (28), 219 (45), 181 (93), 69 (63); HRMS for $C_{24}H_{32}O_8$ calcd 448.2097, found 448.2079. The compound was observed to be spectroscopically identical to that previously reported.[19−23] The optical rotation was observed to be below the rotation measured for the isolated natural product ($[\alpha]^{25}_D = +49.4$)[21] and above all the values previously reported for the synthetic product ($[\alpha]^{25}_D = +21.5$,[22] +26.0,[23] +30.0[23]).

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Supporting Information Available: Copies of ^{1}H NMR spectra (compounds **6**−**13**) and ^{13}C NMR spectra (compounds **6**−**9** and **13**); general experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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