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An Efficient Approach to the Synthesis of 1,3-Diaryl-1,2,3,4-[4*H*]-tetrahydronaphthalene-2-carboxylic Acids

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Abstract—A flexible approach to the synthesis of endothelin receptor antagonists of the 1,3-diaryl-1,2,3,4-[4*H*]-tetrahydronaphthalene-2-carboxylic acid class is described.

Introduction

The endothelins (ETs), discovered in 1988,[1] are a family of three isopeptides (ET-1, ET-2, and ET-3) encoded in the human genome and each is composed of 21 amino acids, with disulfide linkages between cysteine residues at positions 1,15 and 3,11. The ETs elicit their effects through binding to receptors of the G-protein coupled seven-transmembrane spanning superfamily, and two receptor sub-types have been fully characterized from human tissues through molecular cloning and expression.[3–5] Recently, compelling data has become available with receptor specific antagonists to support a role for the ETs in disease processes.[2] Despite extensive animal model studies, controversy still surrounds the optimal antagonist selectivity considered necessary for the treatment of human disorders. This critical question will only be resolved by clinical trials which are now ongoing, and may be dependent upon the disease targeted (Figure 1).

Recently, we reported the rational design and synthesis of 1,3-diarylindane-2-carboxylic acids as potent endothelin antagonists.[6] 209670 (**1**) is a highly potent member of this class which inhibits [^{125}I]ET-1 binding to cloned human ET_A and ET_B receptors with K_i values of 0.43 and 14.7 nM, respectively. Structure–activity relationship studies in the indane series highlight the importance of the all *trans* relationship of aryl, carboxyl and aryl groups for biological activity. As part of our efforts to assess the contribution of the indane ring to antagonist activity, we decided to prepare the analogous tetrahydronaphthalene. To this end Compound **3** was selected as our initial synthetic target in order to compare its biological activities with an earlier lead in the indane series (**2**). In this paper we describe an efficient synthesis of *trans*,*trans*-1,3-diaryltetrahydronaphthalene-2-carboxylic acid (**3**) and demonstrate that this approach can be applied to synthesize other members in this class (Figure 2).

Results and Discussion

Our retrosynthetic analysis for the construction of the 1,3-diaryltetrahydronaphthalene ring system is shown in Scheme 1. Thus the aryl ring at C-1 was envisioned as being added through 1,4-addition-elimination of a Grignard reagent to methyl enol ether (**4**). The methyl enol ether (**4**) would be derived from β-keto ester (**5**) which in turn could be obtained via a Dieckmann cyclization. Finally, it was anticipated that the Dieckmann substrate could be prepared by the fluoride ion promoted Michael addition of trimethylsilylmethylbenzoate (**6**) to benzylidene malonate (**7**)[7] followed by monodeprotection and decarboxylation.

The synthesis (Scheme 2) began with treatment of methyl *o*-trimethylsilylmethylbenzoate (**6**) with a mixture of α,β-unsaturated esters (**7**) in the presence of CsF in dry hexamethylphosphoramide (HMPA), affording the Michael adduct (**8**) in 60% yield. The mixture of

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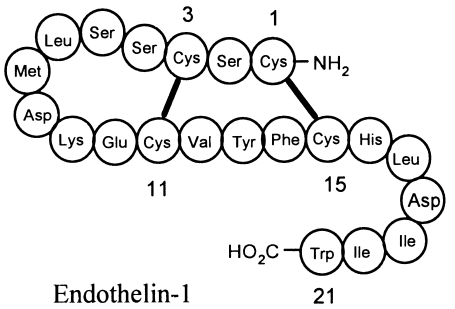
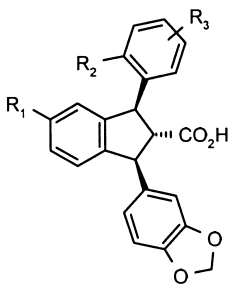


Figure 1.

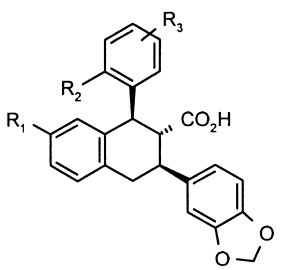
geometric isomers of the arylidene malonate (**7**) was derived by condensation of piperonal and benzylmethyl malonate. Removal of the benzyl protecting group of (**8**) by catalytic hydrogenolysis and subsequent decarboxylation upon heating the mono acid to 150 °C, generated dimethyl ester (**9**) in 96% yield. The β-ketoester (**10**) was then formed as 1:1 mixture of the two possible diastereomers through Dieckmann cyclization with sodium methoxide.[8]

Our initial attempts to install the remaining phenyl substituent at C-1 (Scheme 3) through either, cuprate addition to the methyl enol ether (**11**)[9] or palladium mediated coupling of a boronic acid with the enol triflate (**12**),[10] were unsuccessful. While the major pathway of Grignard addition (i.e., phenyl-magnesium chloride) to the methyl enol ether (**11**) occurred in a 1,2 sense, a small amount of 1,4-addition product was also isolated. We then reasoned that a bulkier alcohol in the ester portion of the molecule should favor the desired 1,4-addition product. α-Methylbenzyl alcohol was chosen since it could be readily removed by hydrogenolysis later in the synthesis. Thus ester exchange with α-methylbenzyl alcohol in the presence of dimethylaminopyridine (DMAP) in refluxing toluene,[11] (Scheme 4) followed by diazomethane treatment of the corresponding phenethyl ester (**13**) in ethanol/diethyl ether, provided methyl enol ether (**14**) in 67% [three steps from (**9**)].

Gratifyingly, addition of 3,4-methylenedioxyphenylmagnesium bromide to the methyl enol ether (**14**) in THF at 0 °C afforded the desired 1,4 addition-elimination product (**15**) in 69% yield. As shown in Table 1,

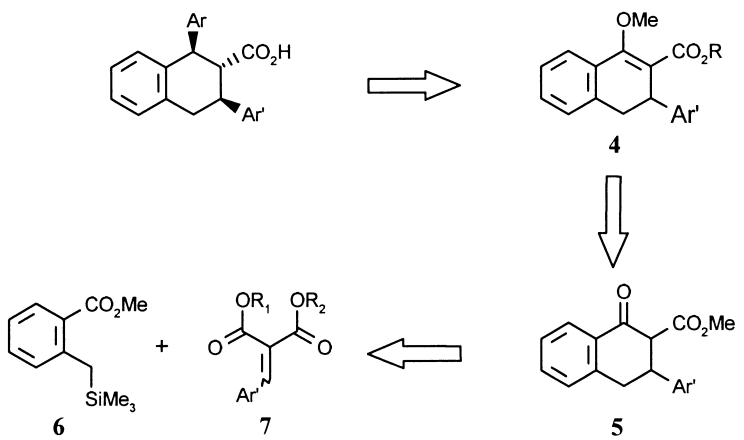


1 R_1 = *n*-Propoxy, R_2 = OCH_2COOH, R_3 = 4-Methoxy
2 R_1 = R_2 = H, R_3 = 3,4-Methylenedioxy

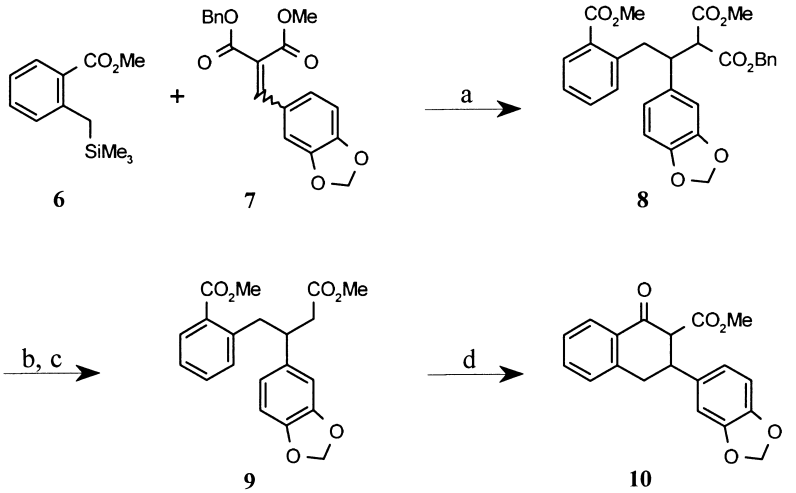


3 R_1 = R_2 = H, R_3 = 3,4-Methylendioxy

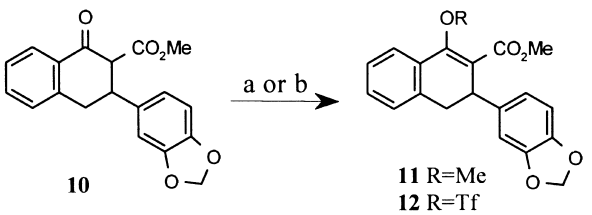
Figure 2.



Scheme 1.



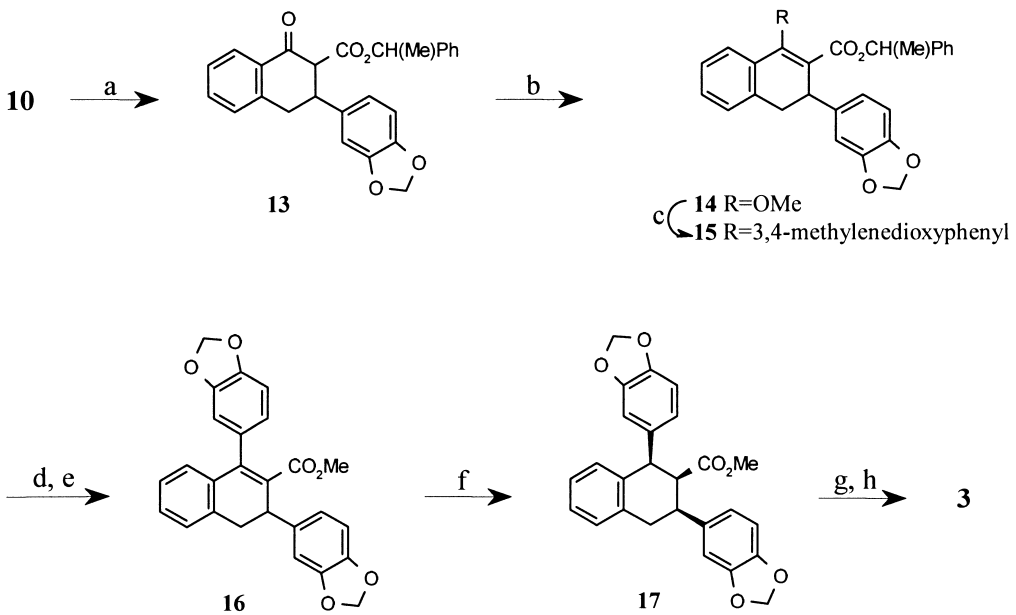
Scheme 2. (a) CsF, HMPA, 60 °C; (b) H_2, 10% Pd/C; (c) 150 °C; (d) NaOMe/MeOH/THF.



Scheme 3. (a) CH_2N_2, MeOH/Diethyl ether or (b) Tf_2O, pyridine, CH_2Cl_2.

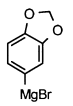
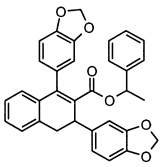
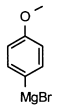
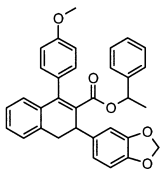
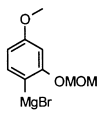
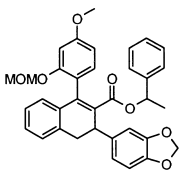
this reaction also proceeds efficiently for other substituted phenyl Grignard reagents as well.

To complete the synthesis of (**3**), the phenethyl ester (**15**) was subjected to hydrogenolysis (10% Pd/C/55 psi-H_2, 5 h) to generate the corresponding acid, which was converted directly to the methyl ester (**16**) in 66% yield for the two steps. Reduction of the tetrasubstituted double bond in (**16**) was then accomplished by further hydrogenation (55 psi) for 72 h to provide all *cis* methyl ester (**17**). Epimerization at C-2 and hydrolysis of the



Scheme 4. Reagents: (a) Ph(Me)CHOH, DMAP, PhMe; (b) CH_2N_2, EtOH; (c) 3,4-Methylenedioxyphenyl-magnesium bromide THF; (d) H_2 (55 psi), 5 h, EtOAc; (e) CH_2N_2, MeOH; (f) H_2 (55 psi), 72 h, EtOAc; (g) MeONa/MeOH, THF; (h) aq NaOH/MeOH, aq HCl.

Table 1. Addition of phenyl Grignard reagents on enol ether **14**

Entry	Grignard reagent	Product	Yield (%)
1		 **15**	69
2		 **18**	70
3		 **19**	64

methyl ester under basic conditions gave the target compound (**3**).

Biological evaluation of (**3**) indicates that it is an inferior antagonist by comparison with the indane counterpart (**2**) [K_i's ETA 1.4 μM (**3**) versus 0.1 μM (**2**); ET_B 3.3 μM (**3**) versus 0.8 μM (**2**)]. The weaker binding affinity of **3** to the receptors might be due to a different conformation presented by the tetrahydronaphthalene ring. Molecular modeling overlay of **2** and **3** (Figure 3) revealed that to keep all three substituents which are important for the binding affinity well aligned, the aromatic ring of **3** is clearly located at a different region compared to that in **2** indicating this aromatic moiety in **2** might also be involved in participating in the interaction with the receptors.

In summary, we have described a flexible approach to *trans*,*trans*-1,3-diaryltetrahydronaphthalene-2-carboxylic acids of type (**3**) from readily available precursors.

Experimental

General methods

Melting points were measured with a Thomas–Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Bruker AM-250 and a Bruker AM-400 spectrometers and are reported as ppm downfield from Me_4Si with multiplicity, number of protons, and coupling constant(s) in Hertz indicated parenthetically. Elemental analyses were obtained using a Perkin–Elmer 240C elemental analyzer. Chromatography refers to flash chromatography using Kiseslgel 60, 230–400 mesh silica gel.

Figure 3. Overlay of indane **2** (red) and tetrahydronaphthalene **3** (green).

Benzyl-methyl-2-[1-(3,4-methylenedioxyphenyl)-2-(2-methylcarboxyphenyl)-ethyl] malonate (8). To a solution of benzyl, methyl-2-(3,4-methylenedioxy-benzyliden)-malonate **7** (2.16 g, 6.35 mmol) and methyl *o*-trimethylsilylmethyl benzoate **6** (2.12 g, 9.53 mmol) in HMPA (6 mL) at room temperature was added CsF (1.93 g, 12.70 mmol) in one portion. The mixture was heated to 60 °C for 3 h under argon and then quenched with water, extracted with 1:1 EtOAc:Hexane. The organic layer was separated and washed with brine and dried ($NaSO_4$). After removing the solvent, chromatography of the residue with 4:1 Hexane:EtOAc gave 1.87 g (60%) of an inseparable 1:1 mixture of title compounds **8** as colorless oil: R_f 0.31 (silica gel, 2:1 *n*-hexane:EtOAc); IR (neat): 2952, 1755, 1723, 1489, 1442, 1248 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.30–3.40 (m, 4H), 3.45 (s, 3H), 3.61 (m, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 3.84 (m, 2H), 4.90 (dd, J = 18 Hz, J = 12.3 Hz, 2H), 5.18 (d, J = 1.2 Hz, 2H), 5.87 (m, 4H), 6.36–6.57 (m, 6H), 7.00–7.40 (m, 16H), 7.50 (d, J = 1.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 168.9, 168.5, 168.4, 167.9, 147.7, 146.7, 140.7, 135.8, 134.1, 134.0, 132.2, 131.8, 130.7, 129.0, 128.8, 128.6, 128.5, 126.6, 122.3, 122.2, 109.0, 108.2, 101.2, 67.7, 67.4, 58.4, 53.0, 52.7, 52.3, 47.7, 38.5, 38.2; MS (ES) m/z 491 (MH^+); Anal. Calcd for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.53; H, 5.33.

Methyl-3-(3,4-methylenedioxyphenyl)-4-(2-methylcarboxyphenyl)butanoate (9). To a solution of triesters **8** (3.30 g,

6.73 mmol) in 10 mL of ethyl acetate was added 330 mg of 10% Pd/C and the mixture was stirred under H_2 atmosphere at room temperature for 7 h. Filtration and concentration gave 2.70 g of the crude acids which were directly used in the following reaction without further purification. ^{1}H NMR ($CDCl_3$): δ 3.30 (m, 2H), 3.52 (s, 3H), 3.54 (m, 4H), 3.80 (s, 3H), 3.81 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 5.79 (m, 4H), 6.44 (m, 2H), 6.54 (m, 4H), 7.00 (m, 2H), 7.11-7.30 (m, 4H), 7.76 (m, 2H). The neat crude acids (2.70 g) were heated to 150 °C for 1 h and flash chromatography of the residue with 4:1 *n*-hexane:ethyl acetate gave 2.30 g (96% over two steps) of the diester **9** as a colorless oil: R_f 0.46 (silica gel, 2:1 *n*-hexane:EtOAc); IR (neat): 2951, 1736, 1721, 1504, 1488, 1438, 1254, 1081, 1039, 811 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.67 (d, J = 8.3 Hz, 2H), 3.23–3.55 (m, 3H), 3.60 (s, 3H), 3.92 (s, 3H), 5.95 (s, 2H), 6.60 (dd, J = 8.0, 1.7 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 7.08 (dd, J = 7.5, 0.8 Hz, 1H), 7.26 (ddd, J = 7.7, 7.7, 1.2 Hz, 1H), 7.37 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.89 (dd, J = 7.8, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 173.0, 168.3, 147.9, 146.4, 141.7, 137.8, 132.3, 132.2, 132.1, 131.2, 130.3, 126.7, 121.1, 108.5, 108.2, 101.2, 52.4, 51.9, 44.0, 41.5, 40.9; MS (ES) m/z 357 (MH^+); Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66. Found: C, 67.42; H, 5.53.

(*RS*)-α-Methylbenzyl–(3*SR*)-1-methoxy-3-(3,4-methylenedioxyphenyl)-3,4-dihydro-2-naphthoate (14). To a solution of diester (800 mg, 2.24 mmol) in 10 mL of THF was added 3 mL of a solution of 25% wt NaOMe/MeOH and the mixture was heated to reflux for 1 h. After cooling to room temperature, the mixture was poured into 1 N HCl and extracted twice with 1:1 hexane:EtOAc. The combined oraginc extract was washed with brine and dried (Na_2SO_4). Removal of the solvent gave the crude β-keto ester **10**, which was used in the next reaction without further purification.

To a solution of the crude β-keto ester **10** in 10 mL of toluene was added α-methylbenzyl alcohol (0.41 mL, 3.36 mmol) and DMAP (10 mg) and the mixture was refluxed for 28 h. After cooling to room temperature, the mixture was poured into water and extracted twice with 1:1 hexane:EtOAc. The combined organic extract was washed with brine and dried (Na_2SO_4). Removal of the solvent gave the crude β-keto ester **13**, which was used in the next reaction without further purification.

To a solution of the crude ester **13** in 10 mL of ethanol at room temperature was added 20 mL of diazomethane solution (13 mmol) and the mixture was stirred under argon at room temperature for 17 h. The reaction was quenched with AcOH and the solution was then concentrated. Flash chromatography of the residue with 4:1 hexane:EtOAc gave 647 mg (67% over three steps) of a 1:1 mixture of inseparable diastereomeric methyl enoethers **14** as colorless oil: R_f 0.56 (silica gel, 3:1 *n*-hexane: EtOAc); IR (neat): 2980, 2934, 1709, 1690, 1616, 1502, 1487, 1441, 1250, 1197, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.44 (d, J = 7.3 Hz, 3H), 1.58 (d, J = 7.3 Hz, 3H), 2.94 (m, 2H), 3.37 (m, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 4.16 (m, 2H), 5.89 (t, 4H), 5.98 (m, 2H), 6.63 (m, 6H), 7.00–7.70 (m, 18H); MS (ES) m/z 429 (MH^+); Anal. calcd for $C_{27}H_{24}O_5$: C, 75.68; H, 5.65. Found: C, 75.34; H, 5.49.

(*RS*)-α-Methylbenzyl-(3*SR*)-1,3-bis(3,4-methylenedioxyphenyl)-3,4-dihydro-2-naphthoate (15). To a mixture of 1-bromo-3,4-methylenedioxy-benzene (423 mg, 2.10 mmol) and Mg (68 mg, 2.80 mmol) in 3 mL of THF was added 2 uL of MeI and the mixture was irradiated by ultrasound for 30 min. To a solution of methyl enol ether **14** (300 mg, 0.70 mmol) in 4 mL of THF at 0 °C under argon was added dropwise the Grignard reagent in THF. After 15 min, the reaction was quenched with aq HCl and the mixture was extracted with 1:1 hexane:EtOAc. The organic extract was washed with brine and dried (Na_2SO_4). After removing the solvent, flash chromatography of the residue with 4:1 hexane:EtOAc gave 250 mg (69%) of 1:1 mixture of inseparable diastereomers **15** as colorless oil: R_f 0.45 (silica gel, 3:1 *n*-hexane:EtOAc); IR (KBr): 2884, 1712, 1692, 1502, 1485, 1437, 1233, 1038, 812, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.18 (d, J = 7.3 Hz, 3H), 1.24 (d, J = 7.3 Hz, 3H), 3.09 (m, 2H), 3.41 (dd, J = 17.3, 7.9 Hz, 2H), 4.15 (m, 2H), 5.67 (m, 2H), 5.91 (s, 4H), 6.00 (m, 4H), 6.68–7.27 (m, 30H); ^{13}C NMR ($CDCl_3$): δ 167.94, 147.43, 146.98, 146.17, 141.28, 136.33, 134.72, 134.61, 132.52, 132.27, 129.05, 128.95, 128.16, 128.10, 128.01, 127.97, 127.74, 127.56, 127.52, 127.47, 126.63, 126.10, 126.04, 122.42, 120.70, 109.77, 108.17, 108.06, 101.01, 100.76, 72.40, 72.38, 41.54, 41.42, 37.21, 37.17, 21.87, 21.60; MS (ES) m/z 519 (MH^+); Anal. calcd for $C_{33}H_{26}O_6$: C, 76.43; H, 5.05. Found: C, 76.70; H, 5.14.

(1*RS*,2*SR*,3*SR*)-Methyl-1,3-bis(3,4-methylenedioxyphenyl)-1,2,3,4-tetrahydro-2-naphthoate (17). To a solution of α-methylbenzylester **15** (454 mg, 0.876 mmol) in 4 mL of EtOAc was added 60 mg of 10% Pd/C and shaken under H_2 (55 psi) at room temperature for 24 h. After filtration and concentration, the residue was dissolved in ether and added excess of diazomethane solution in ether. The reaction was quenched with acetic acid and washed with water, brine and dried (Na_2SO_4). After removing the solvent, flash chromatography of the residue with 4:1 Hexane:EtOAc gave 160 mg (43%) of the *cis–cis* methyl ester **17** as a colorless oil: R_f 0.52 (silica gel, 3:1 *n*-hexane/EtOAc); ^{1}H NMR ($CDCl_3$): δ 2.95 (dd, J = 16.4, 5.0 Hz, 1H), 3.25 (s, 3H), 3.27 (dd, J = 6.3, 3.7 Hz, 1H), 3.37 (m, 1H), 3.86 (t, J = 14.0 Hz, 1H), 4.51 (d, J = 6.3 Hz, 1H), 5.94 (m, 4H), 6.60–7.20 (m, 10H).

(1*RS*,2*SR*,3*SR*)-1,3-Bis(3,4-methylenedioxyphenyl)-1,2,-3,4-tetrahydro-2-naphthoic acid (3). To solution of methyl ester **17** (160 mg, 0.373 mmol) in 3 mL of THF was added 0.7 mL of 25% NaOMe:MeOH and stirred at room temperature under argon for 18 h. The mixture was poured into 1 N HCl and extracted with 1:1 hexane:EtOAc. The organic extract was washed with brine and dried (Na_2SO_4). After removing the solvent, flash chromatography of the residue with 4:1 *n*-hexane:EtOAc gave 130 mg (81%) of the all *trans* methyl ester as a white solid: R_f 0.52 (silica gel, 3:1 *n*-hexane:EtOAc); ^{1}H NMR ($CDCl_3$): δ 3.07 (t, J = 11.2 Hz, 1H), 3.10 (dd, J = 16.7, 5.6 Hz, 1H), 3.20 (dd, J = 16.7, 11.0 Hz, 1H), 3.33 (ddd, J = 11.2, 11.0, 5.6 Hz, 1H), 4.42 (d, J = 11.2 Hz, 1H), 5.96 (s, 4H), 6.55–6.85 (m, 7H), 7.03–7.18 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 173.95, 147.84, 147.62, 146.46, 146.34, 138.07, 137.43, 136.50, 135.70, 129.44, 128.37, 126.28, 122.48, 120.65, 108.98, 108.23, 108.06, 107.71, 100.94, 100.90, 56.98, 51.25, 50.17, 44.14, 38.21; Anal. Calcd for $C_{26}H_{22}O_6$: C, 72.55; H, 5.15. Found: C, 72.52; H, 5.39.

To a solution of all *trans* methyl ester (110 mg, 0.257 mmol) in 6 mL of 1:1 MeOH:THF was added 2 mL of 10% NaOH and heated to 70 °C for 7 h. The mixture was poured into water and washed with 1:1 Hexane:EtOAc. The aqeous solution was acidified with 6 N HCl to pH 5 and extracted with EtOAc. The organic extract was washed with brine and dried (Na_2SO_4). Removal of the solvent gave 100 mg (94%) of the title acid **3** as a white solid: R_f 0.07 (silica gel, 2:1 *n*-hexane:EtOAc); ^{1}H NMR ($CDCl_3$): δ 3.00–3.25 (m, 3H), 4.38 (d, J = 10.8 Hz, 1H), 5.94 (s, 4H), 6.55–7.18 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 177.55, 147.89, 147.69, 146.57, 146.47, 137.84, 137.12, 136.21, 135.60, 129.44, 128.36, 126.35, 122.59, 120.78, 108.96, 108.28, 108.11, 107.68, 100.98, 56.53, 50.05, 43.95, 38.19; MS (ES) m/z 416 (M^+); HRMS (FAB) Calcd for $C_{25}H_{19}O_6Na_2$: 461.0977. Found: 461.0954. Anal. calcd for $C_{25}H_{19}O_6 \cdot H_2O$: C, 69.12; H, 5.10. Found: C, 68.89 H, 5.41.

(*RS*)-Phenethyl-(3*SR*)-1-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-3,4-dihydro-2-naphthoate (18). To a mixture of 1-bromo-4-methoxy benzene (218 mg, 1.17 mmol) and Mg (28 mg, 1.17 mmol) in 3 mL of THF was added 2 μL of MeI and the mixture was irradiated by ultrasound for 30 min. To a solution of methyl enol ether **14** (100 mg, 0.23 mmol) in 4 mL of THF at 0 °C under argon was added dropwise the Grignard reagent solution. After 15 min, the reaction was quenched with aq HCl and the mixture was extracted with 1:1 hexane:EtOAc. The organic extract was washed with brine and dried (Na_2SO_4). After removing the solvent, flash chromatography of the residue with 4:1 hexane:EtOAc gave 83 mg (70%) of 1,4-addition product **18**. ^{1}H NMR ($CDCl_3$): δ 1.08 (d, 3H), 1.17 (d, 3H), 3.02–3.10 (m, 2H), 3.33–3.43 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 5.58–5.65 (m, 2H), 5.88 (s, 4H), 6.60–7.22 (m, 32H).

(*RS*)-Phenethyl-(3*SR*)-1-(2-methoxymethoxy-4-methoxy)-phenyl-3-(3,4-methylene-dioxyphenyl)-3,4-dihydro-2-naphthoate (19). The above procedure was also followed for preparation of 1,4-addition product. Methyl enol ether **14** (44 mg, 0.10 mmol), 4-methoxy-2-methoxymethoxyphenyl megnesium bromide in ether (0.50 mL, 0.10 mmol). Yield 37 mg (64%). ^{1}H NMR ($CDCl_3$): δ 1.12 (d, 3H), 1.22 (d, 3H), 3.02 (m, 2H), 3.19 (s, 3H), 3.23 (s, 3H), 3.50 (m, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.25 (m, 2H), 5.00 (m, 2H), 4.93 (d, 1H), 5.05 (d, 1H), 5.68 (m, 2H), 5.86 (m, 4H), 6.60-7.20 (m, 30H).

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