Formal Synthesis of (−)-*O*-Methylancistrocladine

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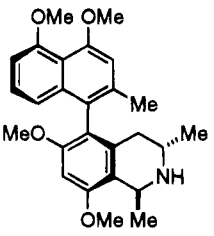
The plant families Dioncophyllaceae and Ancistrocladaceae are the only known sources of the unusual naphthyl-isoquinoline alkaloids, and extracts of these plants have be used in traditional medicine for the treatment of malaria and dysentery.[1] These compounds can be characterized by the location of the linkage between the naphthalene and isoquinoline rings and possess asymmetry associated with restricted rotation about the biaryl bond. Some examples are (−)-*O*-methylancistrocladine (**1**),[2] (+)-dioncophylline C (**2**),[3] the only 5−1′ linked Dioncophyllaceae alkaloid isolated thus far, and the dimeric alkaloid (−)-michellamine A (**3**),[4] which inhibits the cytopathic effects of the AIDS virus *in vitro* and has recently succumbed to total synthesis.[5]



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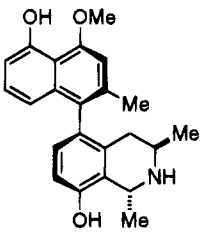

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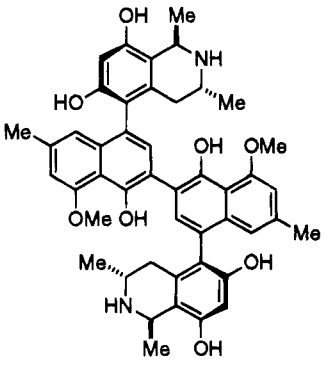

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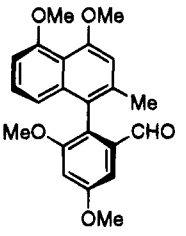

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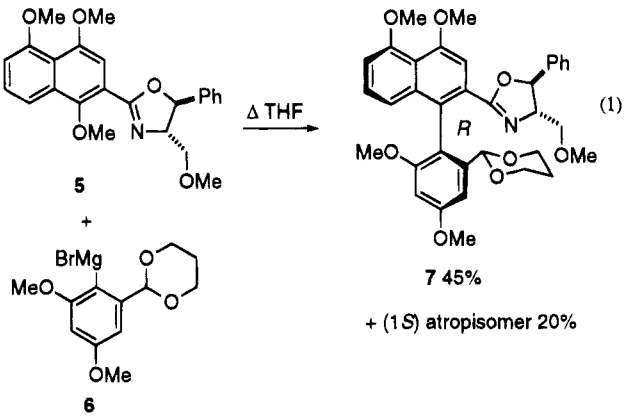
Synthetic strategies toward these alkaloids have been based on both intra- and intermolecular approaches to construct the biaryl linkage.[6] In a synthesis of *O*-methylancistrocladine (**1**) based on an intermolecular approach,[7] the key reaction used to construct the biaryl linkage involved substitution of an aromatic methoxy group by an aryl Grignard reagent in the presence of a chiral oxazoline.[8] A coupling involving the oxazoline **5** and Grignard reagent **6** gave the major atropisomer **7** in low de (38%) which was then converted into alkaloid **1** via aldehyde **4** (eq 1).[7] Although the steric bulk of the 2-



and 6-substituents on the aryl Grignard reagent has some effect on the diastereoselectivity of the coupling reaction,[9] Meyers has recently demonstrated that the stereochemical outcome appears to be dependent on both the steric and electronic effects of the *ortho* substituents on the Grignard reagent.[10] In the example shown in eq 1, the 2- and 6-substituents were apparently able to compete for chelation to magnesium in the transition state[8e,10] and the selectivity was low. Changing one substituent to a nonchelating group (i.e., $CH_2OTBDMS$) should increase the selectivity for the desired atropisomer and we therefore embarked on an improved synthesis of the aldehyde **4**.

The chiral oxazoline **9** required for the coupling reaction was prepared (Scheme 1) by a one-pot procedure[7,8c] that involved treatment of the known amide **8**[7] with triethyloxonium tetrafluoroborate followed by (*S*)-valinol. Silylation of benzyl alcohol **10**[11] gave ether **11**, and the corresponding Grignard reagent was generated using the entrainment method.[12] Addition of a solution of **9** in THF to this Grignard reagent followed by heating under reflux for 15 h afforded the predicted major (*R*)-isomer **12a** (70%) and the minor (*S*)-isomer **12b** (6%) after separation by flash chromatography. The preferred transition state for the coupling can be depicted as rotamer $\mathbf{A}^{\ddagger}$ in which the magnesium atom is chelated to the methoxy group

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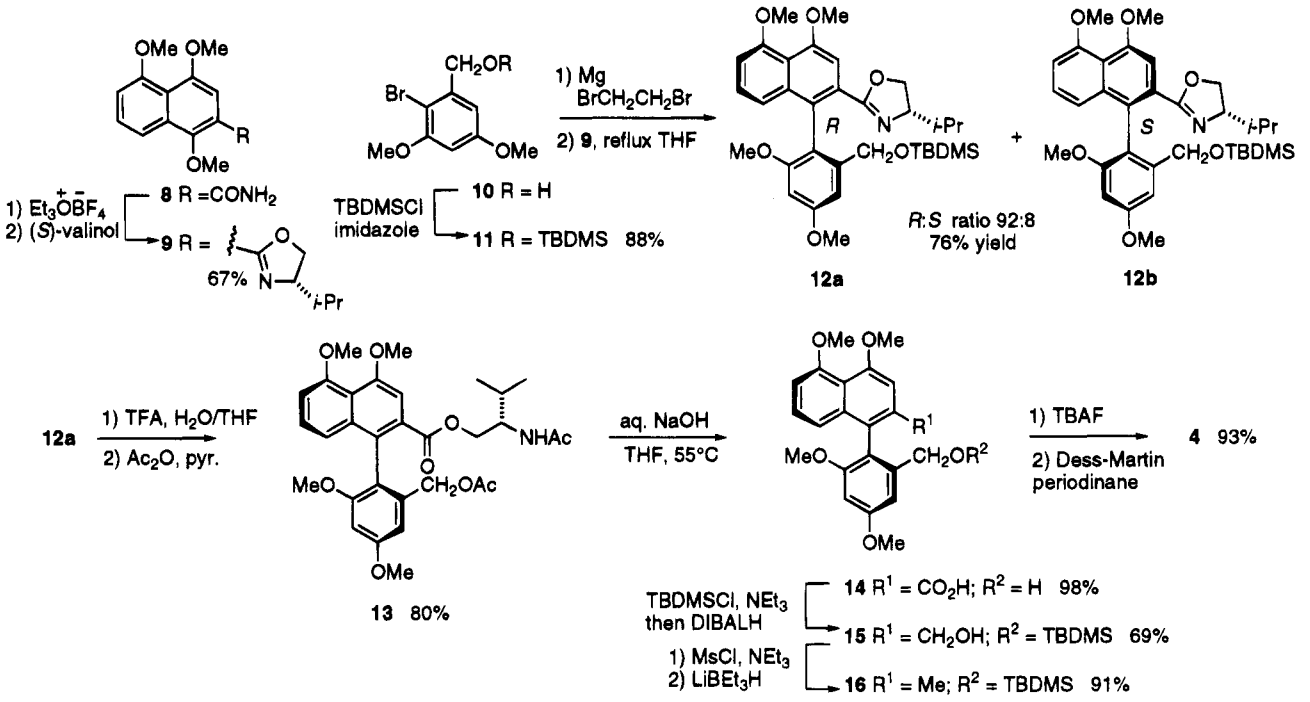
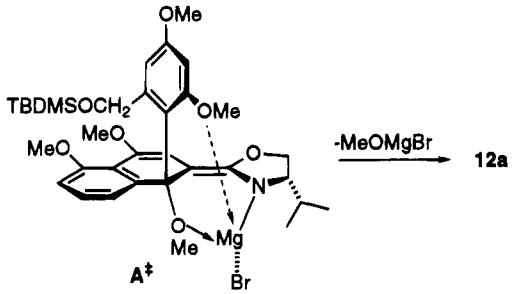
Scheme 1



rather than to the $CH_2OTBDMS$ substituent.[10] Intermediate $\mathbf{A}^{\ddagger}$ then collapses to give the desired biaryl **12a**, and evidence for this outcome was provided by conversion of this atropisomer into the (−)-*O*-methylancistrocladine intermediate **4** (Scheme 1).



Treatment of biaryl **12a** with trifluoroacetic acid in aqueous THF caused ring opening[8b,d] of the oxazoline to give an unstable ammonium salt which was acetylated to provide diacetate **13**. Base hydrolysis of **13** afforded hydroxy acid **14** which was silylated and reduced[8d] to the alcohol **15**. Mesylation followed by reduction with $LiAlH_4$ gave a complex mixture of products from which the desired biaryl **16** was isolated in low yield. Clean reduction of the mesylate derived from alcohol **15** was achieved using $LiBEt_3H$[13] to afford an excellent yield of biaryl **16** which was deprotected and oxidized[14] to give the aldehyde **4**. The physical and spectroscopic data for **4** were identical to that reported in the literature including the sign and magnitude of optical rotation.[7] The high selectivity now attainable for this type of coupling adds to this strategy for the asymmetric synthesis of these natural products.

Experimental Section

General. ^1H NMR (300 MHz) and proton decoupled ^{13}C NMR spectra (75.5 MHz or 100 MHz) were recorded for deuterochloroform solutions with residual chloroform as internal standard. Microanalyses were carried out at the University of Otago, Dunedin, New Zealand. Optical rotations were recorded in a 10 cm microcell. Melting points were measured on a Kofler hotstage apparatus and are uncorrected. Flash chromatography was carried out on Merck silica gel 60. Analytical thin layer chromatography (TLC) was conducted on aluminum backed 2 mm thick silica gel 60 GF_{254} plates supplied by Merck, and chromatograms were visualized with solutions of veratraldehyde and concd H_2SO_4 in ethanol, 20% w/w phosphomolybdic acid in ethanol, or vanillin and concd H_2SO_4 in ethanol. Anhydrous THF was distilled from sodium benzophenone ketyl and potassium metal under a nitrogen atmosphere. All other anhydrous solvents were purified according to standard methods. Petroleum ether refers to the fraction boiling between 60−80 °C.

(−)-(4*S*)-4-Isopropyl-2-(1,4,5-trimethoxy-2-naphthyl)-4,5-dihydrooxazole (9). A solution of triethyloxonium tetrafluoroborate in dichloroethane (1.0 M, 5.7 mL) was added *via* syringe to a solution of **8**[7] (1.0 g, 3.8 mmol) in anhydrous dichloroethane (25 mL) under nitrogen at rt, and the mixture was stirred at rt for 17 h after which time a yellow precipitate had formed. To this suspension was added (*S*)-valinol (0.6 g, 5.8 mmol), and the reaction mixture was heated under reflux for 10 h, cooled, washed with 5% Na_2CO_3, H_2O, and brine, dried, and concentrated to yield a viscous yellow oil. Purification by flash chromatography with 40% EtOAc−petroleum ether as eluent afforded oxazoline **9** (0.85 g, 67%) which crystallized from petroleum ether as pale yellow needles, mp 74.5−75 °C; $[\alpha]^{20}_D$ −58.0° (*c* 1.58, $CHCl_3$); ^1H NMR δ 0.98 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 1.93 (m, 1H,), 3.85 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 4.19 (m, 2H), 4.62 (m, 1H), 6.94 (d, J = 7.8 Hz, 1H), 7.20 (s, 1H), 7.44 (t, J = 8.1 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz) δ 18.2, 19.0, 32.9, 56.5, 56.7, 62.6, 70.0, 72.6, 106.2, 108.2, 115.8, 116.9, 119.8, 127.0, 132.0, 150.0, 152.9, 157.2, 162.2. Anal. Calcd for $C_{19}H_{23}O_4N$: C, 69.32; H, 6.99; N, 4.25. Found: C, 69.12; H, 7.10; N, 4.17.

1-[(*tert*-Butyldimethylsilyloxy)methyl]-2-bromo-3,5-dimethoxybenzene (11). To a stirred solution of **10**[11] (5.46 g, 22 mmol) in dry DMF (100 mL) was added imidazole (3.0 g, 40 mmol) and *tert*-butyldimethylsilyl chloride (5.0 g, 30 mmol) under nitrogen, and the reaction mixture was stirred for 2.5 h at rt and then quenched with H_2O (150 mL). The product was extracted into ether and the organic layer was washed with H_2O and brine and dried ($MgSO_4$). Removal of solvent and purification of the crude product by flash chromatography with 5% EtOAc−petroleum ether as eluent yielded bromide **11** (7.0 g,

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88%) as a colorless oil which solidified as large white plates upon refrigeration: ^{1}H NMR δ 0.14 (s, 6H), 0.98 (s, 9H), 3.81 (s, 3H), 3.86 (s, 3H), 4.73 (s, 2H), 6.40 (d, J = 2.8 Hz, 1H), 6.82 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz) δ −5.4, 18.3, 25.9, 55.4, 56.3, 64.8, 98.2, 100.6, 103.5, 142.5, 156.1, 159.8. Anal. Calcd for $C_{15}H_{25}BrO_3Si$: C, 49.86; H, 6.97; Br, 22.11. Found: C, 49.82; H, 6.93; Br, 22.09.

(−)-(*R*,4*S*)-2-[1-[4,6-Dimethoxy-2-[(*tert*-butyldimethylsilyloxy)methyl]phenyl]-4,5-dimethoxy-2-naphthyl]-4-isopropyl-4,5-dihydrooxazole (12a). A mixture of **11** (2.16 g, 6.0 mmol) and magnesium turnings (0.29 g, 12 mmol) in anhydrous THF (20 mL) was heated at reflux under nitrogen, and a solution of 1,2-dibromoethane (0.52 mL, 6.0 mmol) in anhydrous THF (7 mL) was added dropwise over 20 min. The mixture was boiled for a further 1 h and then cooled to rt. To the resulting Grignard reagent was added a solution of **9** (1.0 g, 3.1 mmol) in THF (10 mL) *via* cannula. The solution was then heated at reflux for 15 h, cooled, and then quenched with saturated NH_4Cl, and the product was extracted with EtOAc. Removal of the solvent left the crude product which was chromatographed over silica gel using 40% EtOAc−petroleum ether as eluent to afford the major biaryl **12a** (1.26 g, 70%) as a yellow gum: $[\alpha]^{25}_D$ −48.4° (*c* 2.0, $CHCl_3$); ^{1}H NMR δ −0.18 (s, 3H), −0.14 (s, 3H), 0.76 (d, J = 6.6 Hz, 3H), 0.82 (s, 9H) 0.82 (d, J = 6.6 Hz, 3H), 1.60 (oct, J = 6.6 Hz, 1H), 3.55 (s, 3H), 3.71−4.13 (m, 4H) 3.89 (s, 3H), 3.98 (s, 3H), 4.05 (s, 3H), 4.38 (d, J = 14.4 Hz, 1H), 6.43 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 7.22 (t, J = 8.1 Hz, 1H), 7.27 (s, 1H); ^{13}C NMR (75.5 MHz) δ −5.5, 18.1, 18.2, 18.6, 25.8, 32.6, 55.2, 55.9, 56.3, 56.6, 62.7, 70.1, 72.5, 96.9, 101.6, 106.2, 107.5, 117.7, 118.6, 119.4, 126.7, 126.8, 127.0, 136.3, 143.1, 156.3, 157.1, 158.2, 160.2, 164.2; HRMS calcd for $C_{33}H_{45}NO_6Si$ 578.2938, found 578.2950.

Further elution yielded the minor biaryl **12b** (113mg, 0.19mmol, 6%) as a yellow glass: ^{1}H NMR δ −0.16 (s, 3H), −0.13 (s, 3H), 0.78 (d, J = 6.6 Hz, 3H), 0.82 (s, 9H), 0.84 (d, J = 7.5 Hz, 3H), 1.64 (oct, J = 6.6 Hz, 1H), 3.56 (s, 3H), 3.57−4.07 (m, 3H), 3.89 (s, 3H), 3.98 (s, 3H), 4.05 (s, 3H), 4.33 (d, J = 14.7 Hz, 1H), 6.43 (d, J = 2.1 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.20 (t, J = 8.1 Hz, 1H).

(−)-(*R*, 2*S*)-2-(Acetylamino)-3-methylbutyl 1-[2′-[(Acetyloxy)methyl]-4′,6′-dimethoxyphenyl]-4,5-dimethoxynaphthalene-2-carboxylate (13). To a solution of **12a** (1.09 g, 3.54 mmol) in anhydrous THF (20 mL) were added powdered anhydrous Na_2SO_4 (14 g), H_2O (1.8 mL) and trifluoroacetic acid (0.77 mL). The yellow suspension was stirred at rt for 24 h, and then an additional amount of anhydrous Na_2SO_4 (5 g) was added. Filtration and concentration under reduced pressure at <30 °C gave an unstable ammonium salt which was dissolved in CH_2Cl_2 (30 mL), cooled to 0 °C, and treated sequentially with acetic anhydride (6.5 mL) and pyridine (9.6 mL) under nitrogen. The reaction mixture was allowed to warm to rt over 4 h and then washed with cold 10% HCl, saturated $NaHCO_3$, H_2O, and brine. Removal of solvent left a yellow viscous oil which was purified by flash column chromatography with 80% EtOAc−petroleum ether as eluent to afford amide **13** (0.86 g, 80%) as a white foam; $[\alpha]^{25}_D$ −98.1° (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 0.80 (d, J = 6.3 Hz, 3H), 0.82 (d, J = 6.3 Hz, 3H), 1.25 (m, 1H), 1.89 (s, 3H), 1.93 (s, 3H), 3.59 (s, 3H), 3.77 (m, 1H), 3.90 (s, 3H), 4.00 (dd, J = 11.7, 3 Hz, 1H), 3.97 (s, 3H), 4.06 (s, 3H), 4.30 (dd, J = 11.7, 3.3 Hz, 1H), 4.55 (ABq, J = 12.9 Hz, 2H), 5.26 (d, J = 9.6 Hz, 1H), 6.58 (d, J = 2.7 Hz, 1H), 6.68 (d, J = 2.7 Hz, 1H), 6.77 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 7.24 (dd, J = 8.1, 7.5 Hz, 1H), 7.46 (s, 1H); ^{13}C NMR (75.5 MHz) δ 19.2, 19.4, 20.6, 23.0, 28.1, 53.1, 55.3, 55.7, 56.3, 56.7, 64.4, 65.9, 97.8, 104.7, 106.3, 108.4, 119.3, 119.5, 121.1, 126.5, 127.2, 129.0, 136.5, 136.6, 156.9, 157.4, 158.6, 160.1, 168.2, 169.6, 170.5. Anal. Calcd for $C_{31}H_{37}O_9N$: C, 65.60; H, 6.57; N, 2.47. Found: C, 65.37; H, 6.57; N, 2.56.

(−)-(*R*)-1-[1-(Hydroxymethyl)-3,5-dimethoxy-2-phenyl]-4,5-dimethoxynaphthyl-2-carboxylic Acid (14). A solution of **13** (0.56 g, 0.99 mmol) in THF (25 mL), H_2O (20 mL) and aqueous NaOH (2.5 M, 2.6 mL) was heated at 55 °C for 3.5 h. The mixture was then cooled to rt, and the THF was removed under reduced pressure. The opaque aqueous layer was washed with chloroform, cooled, and acidified using 10% HCl, and the product was extracted with CH_2Cl_2. Removal of the solvent gave acid **14** (0.39 g, 98%) as a white foam: $[\alpha]^{23}_D$ −46.9° (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 3.56 (s, 3H), 3.88 (s, 3H), 3.97 (s, 3H), 4.02 (s, 3H), 4.13 (s, 3H), 6.53 (d, J = 2.1 Hz, 1H), 6.71 (d, J = 2.1 Hz, 1H), 6.90 (t, J = 8.7 Hz, 1H), 7.23−7.28 (m, 3H); ^{13}C NMR (75.5 MHz) δ 55.3, 55.8, 56.3, 56.6, 63.6, 98.5, 104.9, 105.4, 108.3, 119.0, 119.3, 127.2, 127.3, 130.1, 136.6, 140.6, 156.6, 157.2, 158.3, 160.6, 171.6; HRMS calcd for $C_{22}H_{22}O_7$ 398.1365, found 398.1374.

(−)-(*R*)-2-[2-[2-(Hydroxymethyl)-4,5-dimethoxy-1-naphthyl]]-3,5-dimethoxy-1-[(*tert*-butyldimethylsilyloxy)methyl]benzene (15). A solution of the **14** (0.37 g, 0.94 mmol) in dry CH_2Cl_2 (8.4 mL) was treated sequentially with dry triethylamine (0.45 mL, 3.2 mmol), *tert*-butyldimethylsilyl chloride (0.43 g, 2.8 mmol), and a spatula tip of DMAP at 0 °C under nitrogen. The mixture was stirred at ambient temperature for 2.5 h, resulting in a pale yellow solution which was cooled to −78 °C, and a solution of DIBALH in toluene (1.5 M, 5.4 mL) was added dropwise *via* syringe. The solution was stirred for 1 h at −78 °C and then treated with EtOAc (4.5 mL), CH_2Cl_2 (11 mL), and potassium tartrate (0.5 M, 42 mL), and the resulting mixture was stirred at rt overnight. The organic layer was washed with H_2O and concentrated to give the crude product which was flash chromatographed with 40% EtOAc−petroleum ether as eluent. Recrystallization from petroleum ether afforded alcohol **15** (0.32 g, 69%) as prisms, mp 129−130 °C; $[\alpha]^{25}_D$ −53.4° (*c* 2.0, $CHCl_3$); ^{1}H NMR δ −0.14 (s, 3H), −0.13 (s, 3H), 0.79 (s, 9H), 2.55 (br s, 1H), 3.61 (s, 3H), 3.90 (s, 3H), 3.98 (s, 3H), 4.04 (ABq, J = 12 Hz, 2H), 4.05 (s, 3H), 4.34 (br s, 2H), 6.55 (d, J = 2.4 Hz, 1H), 6.82−6.84 (m, 3H), 7.06 (s, 1H), 7.20 (dd, J = 8.1 Hz, 1H); ^{13}C NMR (100 MHz) δ −5.6, 18.2, 25.8, 55.2, 55.8, 56.2, 56.4, 62.9, 64.1, 97.8, 104.0, 106.2, 106.8, 117.2, 117.6, 118.3, 123.8, 126.5, 136.4, 137.9, 142.3, 156.9, 157.3, 158.0, 160.4. Anal. Calcd for $C_{28}H_{38}O_6Si$: C, 67.44; H, 7.68. Found: C, 67.33; H, 7.57.

(−)-(*S*)-2-(4,5-Dimethoxy-2-methyl-1-naphthyl)-3,5-dimethoxy-1-[(*tert*-butyldimethylsilyloxy)methyl]benzene (16). A solution of methanesulfonyl chloride (230 μL, 0.30 mmol) in dry CH_2Cl_2 (1.6 mL) was added dropwise at 0 °C to a solution of **15** (100 mg, 0.2 mmol) and triethylamine (560 mL, 0.4 mmol) in CH_2Cl_2 (3 mL). The solution was allowed to stir at 0 °C for 40 min and then diluted with EtOAc (30 mL) and H_2O, and the organic layer was washed with 10% HCl, saturated $NaHCO_3$, and H_2O. Removal of the solvent gave the crude mesylate (116 mg, 100%) as a white foam which was dissolved in anhydrous THF (0.5 mL), cooled to 0 °C, and treated with $LiBEt_3H$ (0.62 mL, 1 M in THF). The reaction was then allowed to warm to rt, stirred for 2 h, and cooled to 0 °C, and the excess hydride was quenched with H_2O and the product was extracted with EtOAc. Purification of the crude product by flash chromatography with 20% EtOAc−petroleum ether as eluent gave ether **16** (88 mg, 91%) as white plates following recrystallization from petroleum ether: mp 91−91.5 °C; $[\alpha]^{23}_D$ −35.5° (*c* 1.8, $CHCl_3$); ^{1}H NMR δ −0.15 (s, 3H), −0.14 (s, 3H), 0.83 (s, 9H), 2.08 (s, 3H), 3.61 (s, 3H), 3.91 (s, 3H), 3.97 (s, 3H), 4.01 (s, 3H), 4.08 (ABq, J = 12 Hz, 2H), 6.51 (d, J = 2.4 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.79 (s, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.1, 7.8 Hz, 1H); ^{13}C NMR (100 MHz) δ −5.6, −5.5, 18.2, 20.4, 25.8, 55.2, 55.7, 56.2, 56.4, 62.5, 97.2, 102.2, 105.2, 108.8, 116.1, 117.9, 118.0, 124.3, 126.2, 135.1, 136.4, 142.5, 156.0, 157.2, 158.0, 160.1. Anal. Calcd for $C_{28}H_{38}O_5Si$: C, 69.67; H, 7.94. Found: C, 69.55; H, 8.11.

(+)-(*S*)-2-(4,5-Dimethoxy-2-methyl-1-naphthyl)-3,5-dimethoxybenzaldehyde (4). A solution of **16** (88 mg, 0.18 mmol) and tetrabutylammonium fluoride (140 mg, 0.55 mmol) in anhydrous THF (3 mL) was stirred at rt for 1 h. H_2O was added, and the product was extracted with EtOAc and concentrated under reduced pressure to give the crude alcohol (67 mg, 100%) which was dissolved in dry CH_2Cl_2 (2 mL) and treated with Dess−Martin periodinane[14] (130 mg, 0.31 mmol). After stirring at rt for 25 min, the solution was diluted with ether, and stirred with saturated $NaHCO_3$ and 1.5 M $Na_2S_2O_3$. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to give the crude product which was purified by flash chromatography using 20% EtOAc−petroleum ether as eluent to afford aldehyde **4** which crystallized from CH_2Cl_2−petroleum ether as pale yellow prisms (62 mg, 93%): mp 151−153 °C, lit.[7] mp 152−154 °C. $[\alpha]^{23}_D$ +6.8° (*c* 1.2, THF), lit.[7] $[\alpha]_D$ +8.0° (*c* 1.2, THF); ^{1}H NMR δ 2.11 (s, 3H), 3.66 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 4.01 (s, 3H), 6.74−6.80 (m, 3H), 6.85 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 8.4,

8.1 Hz, 1H), 9.33 (s, 1H); ^{13}C NMR (100 MHz) δ 20.9, 55.6, 56.0, 56.3, 56.5, 100.5, 105.3, 105.5, 108.5, 116.0, 118.5, 121.3, 126.8, 126.9, 136.3, 136.4, 137.5, 156.8, 157.3, 159.0, 160.3, 192.5; HRMS calcd for $C_{22}H_{22}O_5$ 366.1467, found 366.1462.

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Supporting Information Available: Copies of 300 MHz ^1H NMR spectra of compounds **4**, **12a**, **12b**, **13**, **14**, **15**, and **16** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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