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Facile Synthesis of Natural Alkoxynaphthalene Analogues from Plant Alkoxybenzenes

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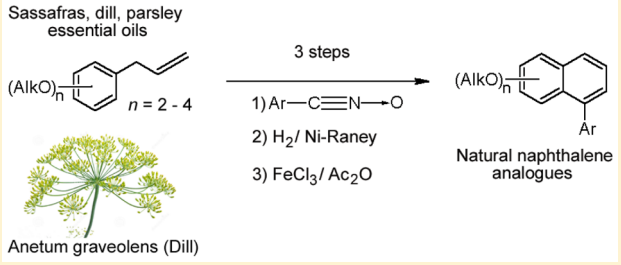
Supporting Information

ABSTRACT: Analogues of the bioactive natural alkoxynaphthalene pycnanthulignene D were synthesized by an efficient method. The starting plant allylalkoxybenzenes (**1**) are easily available from the plant essential oils of sassafras, dill, and parsley. The target 1-arylalkoxynaphthalenes (**5**) exhibited antiproliferative activity in a phenotypic sea urchin embryo assay.



Natural products with alkoxynaphthalene cores (Figure 1) are components of the liverworts *Adelanthus decipiens*

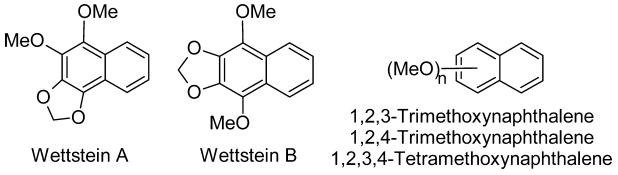


Figure 1. Structures of plant alkoxynaphthalenes.

(Hook.) Mitt. (Adelanthaceae), a scarce species of the British Isles and South America, and *Wettsteinia schusterana* Grolle (Adelantaceae) from New Zealand.[1,2]

Natural alkoxy-1-arylnaphthalenes are very rare. There is only one example of a 1-arylnaphthalene, pycnanthulignene D, with four alkoxy groups in ring A (Figure 2). This compound was isolated from the tree *Pycnanthus angolensis* (Welw.) Warb. (Myristicaceae), which grows throughout western and central Africa.[3] The leaves, roots, wood, and bark of this plant have been used as folk remedies in Cameroon to treat rhinitis,[4] stomachache,[5] and chest pains.[6] The application of *P. angolensis* in traditional medicines for the treatment of malaria,[6] toothache,[7] fungal and worm infections,[8,9] and leprosy[9] was also reported. Recently, it was found that synthetic polyoxygenated 1-arylnaphthalene **I** and dihydronaphthalene **II** (Figure 2) exhibited cytotoxicity against human cancer cell lines at nanomolar concentrations that was associated with the inhibition of tubulin polymerization.[10] Their molecular skeleton is similar to that of the potent tubulin polymerization inhibitor iso-combretastatin A-4 (iso-CA4) (Figure 2).[11]

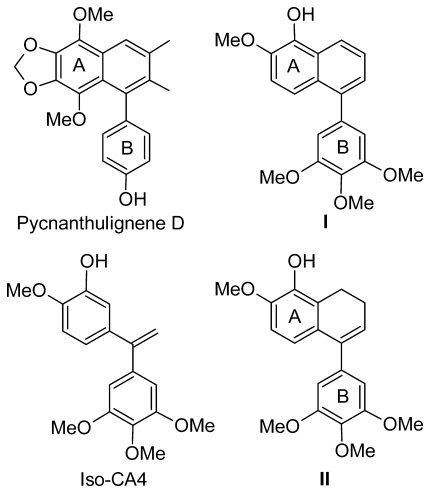


Figure 2. Structures of 1-arylalkoxynaphthalenes and iso-CA4.

Synthesis of highly oxygenated 1-arylnaphthalenes in both rings A and B is a promising approach to the development of molecules with various bioactivities. There are different approaches to the synthesis of 1-arylnaphthalenes. However, all of them are rather complicated, particularly due to the multiple synthetic steps necessary for the construction of alkoxybenzene, naphthalene, and 1-bromonaphthalene rings as well as the preparation of noncatalogued boronic acid derivatives.[10,12−18] Moreover, a number of reported synthetic routes have afforded some byproducts. To simplify the

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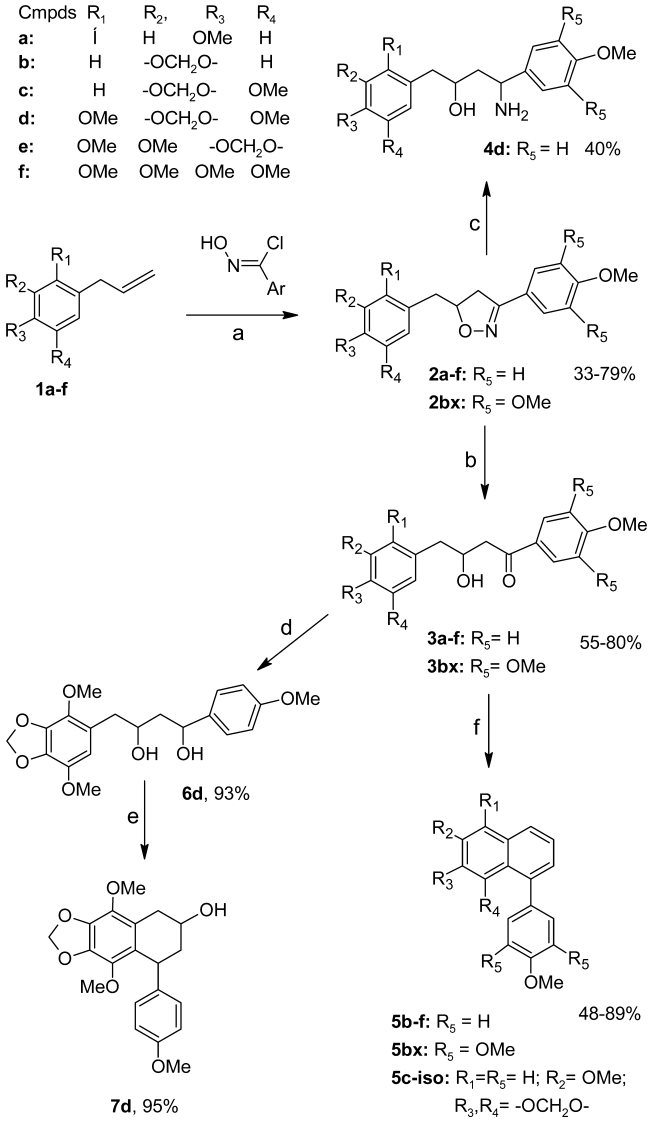
procedure, readily available plant allylalkoxybenzenes were applied as reliable natural building blocks for the synthesis of alkoxysubstituted 1-arylnaphthalenes. Different plants, including cultivated species, contain these metabolites in significant amounts. Allylalkoxybenzenes **1** (Scheme 1) can be isolated by

Scheme 1[a]



[a]Reagents and conditions: (a) Et_3N, CH_2Cl_2, 10−20 °C, 15 h, **2a−f** refs 26,27 **2bx** ref 28; (b) MeOH−H_2O (10:1:1 v/v), H_3BO_3, Raney Ni, 1 atm, rt, 24 h; (c) THF−AcOH−H_2O (10:1:1 v/v), Raney Ni, 20 atm, rt, 24 h; (d) MeOH, $NaBH_4$, rt, 1 h; (e) benzene, *p*-TsOH, rt, 0.5 h; (f) Ac_2O, $FeCl_3$, rt, 0.5 h.

vapor distillation, or liquid CO_2 extraction followed by high-efficiency large-scale distillation.[19,20] The essential oil of tarragon [*Artemisia dracunculus* L. (Asteraceae)] contains 60−75% methylchavicol (estragole, **1a**).[21] Sassafras oil extracted from *Sassafras albidum* (Nuttt.) Nees (Lauraceae), a tree growing in eastern North America, is the main natural source for safrole (**1b**) (85%).[22] Oil from the seeds of dill [*Anethum graveolens* L. (Apiaceae)], cultivated in India, contains 33% dillapiol (**1e**).[19] Parsley [*Petroselinum sativum* Hoffm. (Apiaceae)] seed extracts are a versatile source of allylalkoxybenzenes. Specifically, essential oils from different parsley varieties cultivated in Russia contain myristicin (**1c**) (46%), apiol (**1d**) (60−75%), and allyltetramethoxybenzene (**1f**) (10−20%).[19]

RESULTS AND DISCUSSION

In the present study, a short universal method for the synthesis of 1-arylalkoxynaphthalenes **5** was developed, starting from alkoxybenzenenitrile oxides and allylbenzenes **1** (Scheme 1). Dihydroisoxazoles (**2**) were synthesized from allylbenzenes **1** and nitrile oxides, which were generated in situ from hydroxymoyl chlorides using Et_3N as a base. The isoxazolines **2** were then converted to hydroxy ketones **3** by catalytic hydrogenation with Raney nickel at 1 atm according to the published procedure[23] with a modification; namely, the solvent H_2O−AcOH−THF was replaced by H_2O−MeOH−H_3BO_3. However, during the reaction, minor impurities of the corresponding amino alcohols **4** were formed. Catalytic hydrogenation of isoxazoline **2d** with Raney nickel at higher pressure (20 atm) in the same solvents resulted in the amino alcohol **4d** as a main product. The chemoselective reduction of isoxazolines **2** to the corresponding hydroxy ketones (**3**) could be achieved using a facile, economical, and efficient protocol with Fe/NH_4Cl as a reducing agent.[24] However, in this case, the compound yields depend on the quality of the iron powder. Hydroxy ketone **3d** was hydrogenated in high yield to diol **6d** followed by cyclization to hydroxytetrahydronaphthalene **7d** in the presence of *p*-TsOH. Notably, the cyclization of amino alcohol **4d** to **7d** was unsuccessful. Direct Perkin cyclization of hydroxy ketones **3** followed by aromatization with removal of H_2O afforded the target 1-arylnaphthalenes **5**. It is worth noting that the allyl group of allylbenzenes **1** was used for the construction of the benzene ring in naphthalenes **5**; therefore none of carbon atoms were missing during the three-step transformation. This procedure for the synthesis of 1-arylnaphthalenes **5** is more simple than the cyclization of arylidene-*β*-benzoylpropionic acid in acidic media in the mixture of HCl, H_2SO_4, and H_3PO_4,[12,25] as well as the cyclization of *γ*-benzoylpropylbenzenes to 1-arylnaphthoic acid in aqueous AcOH.[14,25] It should be noted that the hydroxy ketone derivative **3a**, with one methoxy group in benzene ring A, failed to cyclize to the respective 1-arylnaphthalene due to a lack of electron donor substituents in the benzene ring.

The structures of the naphthalenes **5** were proved by MS, ^{1}H NMR, and ^{13}C NMR analyses. For **5b**, the spectroscopic data were compared with those of this compound synthesized by another procedure.[18] The cyclization of hydroxy ketones **3** to the 1-arylnaphthalene system was proved by measuring the NOE signals. In the 2D ^{1}H NMR NOESY spectra of compounds **5b−f**, cross-peaks between proton signals in the aromatic rings were observed (Figure 3). The formation of two isomers, **5c** and **5c-iso**, during the cyclization of **3c** was proved by proton assignments made in the 2D ^{1}H NMR NOESY spectra.

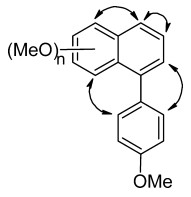


Figure 3. Key cross-peaks in the 2D ^{1}H NMR NOESY spectra of compounds **5b−f**.

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Intermediates and targeted 1-arylnaphthalenes were evaluated for antiproliferative activity using a phenotypic sea urchin embryo assay.[29] It was reported previously that compounds **2d** and especially **2e** immobilized sea urchin embryos due to a selective detachment of motile cilia from the embryo surface.[27] Intermediates **3c** and **3b**, byproduct **4d**, and naphthalenes **5b**, **5c-iso**, **5d**, and **5f** were inactive up to a 4 μM concentration. Compounds **5c**, **5e**, and **5bx** caused cleavage alteration at threshold concentrations of 4, 1, and 2 μM, respectively. Intermediate **6d** altered the sea urchin embryo cleavage at a threshold concentration of 2 μM. However, the cyclization of **6d** yielded inactive tetrahydronaphthalene **7d**.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were measured on a Boetius melting point apparatus and were uncorrected. Reaction mixtures were stirred magnetically. ^{1}H NMR spectra were recorded on a Bruker DRX-500 (500.13 MHz) instrument. Chemical shifts are stated in parts per million (ppm) and referenced to the appropriate NMR solvent peak(s). 2D NMR experiments {^{1}H−^{1}H} NOESY, {^{1}H−^{13}C} HMBC-qs, and {^{1}H−^{13}C} HSQC were used where necessary in assigning NMR spectra. Spin−spin coupling constants (J) were reported in hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker DRX-500 (75.47 MHz) instrument. Chemical shifts are stated in parts per million and referenced to the appropriate solvent peak(s) and were assigned as C, CH, CH_2, and CH_3 as determined using HSQC and HMBC 2D NMR experiments, where necessary. Spin−spin coupling constants were reported in hertz. Low-resolution mass spectra (m/z) were recorded on a Finnigan MAT/INCOS 50 mass spectrometer at 70 eV using direct probe injection. Elemental analysis was performed on the automated PerkinElmer 2400 CHN microanalyzer. Flash chromatography was carried out on silica gel (Acros, 0.035−0.070 mm, 60 Å). TLC was performed on Merck 60 F_{254} plates.

Non-anhydrous solvents and all reagents were purchased at the highest commercial quality and used as received. The starting materials estragole (**1a**), safrole (**1b**), and 3,4,5-trimethoxybenzaldehyde were purchased from Acros Organics (Belgium). Isolation of essential oils containing allylalkoxybenzenes **1c−f** was carried out by liquid CO_2 extraction of parsley and dill seeds by Karawan Ltd. (Krasnodar, Russia).[19] The seed essential oils of parsley varieties cultivated in Russia contained myristicin (**1c**) (40−46%, var. Astra), apiol (**1d**) (70−75%, var. Sakharnaya), and allyltetramethoxybenzene (**1f**) (18−21%, var. Slavyanovskaya). The Indian and Uzbekistan dill seed essential oils contained dillapiol (**1e**) (30−33%). Allylmethoxybenzenes **1c−f** with 98−99% purity were obtained by high-efficiency distillation using a pilot plant device at the N. D. Zelinsky Institute of Organic Chemistry RAS (Moscow, Russia).

General Procedure for the Synthesis of Isoxazolines 2a−f. 4-Methoxybenzylhydroxymoyl chloride used in the preparation of **2a−f** was prepared according to the reported procedure.[30] A solution of triethylamine (8.57 g, 84.7 mmol) in 100 mL of methylene dichloride was added for 4 h to a solution containing allylbenzene (92.4 mmol) and 4-methoxybenzylhydroxymoyl chloride (14.29 g, 77.0 mmol) in 300 mL of methylene dichloride at 0−5 °C. The reaction was stirred at +10 °C for 3 h, then at room temperature for 10 h, washed with water (1 × 100 mL), and evaporated under vacuum. Recrystallization of the oil from EtOAc−hexane (1:1 v/v) yielded a white solid powder of isoxazolines **2a−f**.

*3-(4-Methoxyphenyl)-5-(4-methoxybenzyl)-4,5-dihydroisoxazole (**2a**):* 13.05 g, 57% yield; white solid; mp 138−139 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.58 (2H, d, J = 8.8 Hz, H-2′,6′), 7.22 (2H, d, J = 8.8 Hz, H-3′,5′), 6.98 (2H, d, J = 8.8 Hz, H-2″,6″), 6.87 (2H, d, J = 8.8 Hz, H-3″,5″), 4.84 (1H, m, H-5), 3.79 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.37 (1H, dd, J = 16.8 Hz, J = 10.2 Hz, H-4), 3.04 (1H, dd, J = 16.8 Hz, J = 7.9 Hz, H-4), 2.91 (1H, dd, J = 13.9 Hz, J = 6.6 Hz, CH_2Ar), 2.80 (1H, dd, J = 13.9 Hz, J = 6.6 Hz, CH_2Ar); EIMS m/z 297 [M]$^+$ (15), 176 (100), 121 (17), 92 (12), 77 (26); anal. C 72.71; H 6.44; N 4.71%, calcd for $C_{18}H_{19}NO_3$, C 72.78; H 6.48; N 4.67%.

*5-[(1,3-Benzodioxol-5-yl)methyl]-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**2b**):* 14.87 g, 62% yield; white solid; mp 79−81 °C; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.58 (2H, d, J = 8.8 Hz, H-2′,6′), 6.98 (2H, d, J = 8.8 Hz, H-3′,5′), 6.91 (1H, d, J = 1.5 Hz, H-4″), 6.84 (1H, d, J = 7.9 Hz, H-7″), 6.75 (1H, dd, J = 7.9 Hz, J = 1.5 Hz, H-6″), 5.97 (2H, m, OCH_2O), 4.84 (1H, m, H-5), 3.79 (3H, s, OCH_3-4′), 3.37 (1H, dd, J = 16.9 Hz, J = 10.3 Hz, H-4), 3.05 (1H, dd, J = 16.9 Hz, J = 7.9 Hz, H-4), 2.90 (1H, dd, J = 13.8 Hz, J = 6.6 Hz, CH_2Ar), 2.78 (1H, dd, J = 13.8 Hz, J = 6.7 Hz, CH_2Ar); EIMS m/z 311 [M]$^+$ (33), 176 (24), 148 (12), 136 (53), 135 (100), 121 (25), 77 (41); anal. C 69.44; H 5.50; N 4.50%, calcd for $C_{18}H_{17}NO_4$, C 69.37; H 5.47; N 4.55%.

*5-[(7-Methoxy-1,3-benzodioxol-5-yl)methyl]-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**2c**):* 17.87 g, 68% yield; white solid; mp 103−105 °C (EtOAc−hexane, 1:2); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.59 (2H, d, J = 8.8 Hz, H-2′,6′), 6.99 (2H, d, J = 8.8 Hz, H-3′,5′), 6.60 (1H, s, H-4″), 6.58 (1H, s, H-6″), 5.95 (2H, s, OCH_2O), 4.86 (1H, m, H-5), 3.81 (3H, s, OCH_3-7″), 3.79 (3H, s, OCH_3-4′), 3.36 (1H, dd, J = 17.0 Hz, J = 10.2 Hz, H-4), 3.08 (1H, dd, J = 17.0 Hz, J = 7.8 Hz, H-4), 2.91 (1H, dd, J = 13.6 Hz, J = 6.4 Hz, CH_2Ar), 2.77 (1H, dd, J = 13.6 Hz, J = 6.9 Hz, CH_2Ar); EIMS m/z 341 [M]$^+$ (15), 176 (24), 166 (72), 165 (100), 148 (11), 121 (28), 92 (19), 77 (30); anal. C 66.85; H 5.61; N 4.10%, calcd for $C_{19}H_{19}NO_5$, C 66.69; H 5.53; N 4.05%.

*5-[(4,7-Dimethoxy-1,3-benzodioxol-5-yl)methyl]-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**2d**):* 22.31 g, 78% yield; white solid; mp 102−103 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.60 (2H, d, J = 8.8 Hz, H-2′,6′), 7.00 (2H, d, J = 8.8 Hz, H-3′,5′), 6.58 (1H, s, H-6″), 5.99 (1H, s, OCH_2O), 5.98 (1H, s, OCH_2O), 4.83 (1H, m, H-5), 3.82 (3H, s, OCH_3), 3.80 (3H, s, OCH_3-4′), 3.77 (3H, s, OCH_3), 3.36 (1H, dd, J = 17.0 Hz, J = 10.2 Hz, H-4), 3.08 (1H, dd, J = 17.0 Hz, J = 7.4 Hz, H-4), 2.89 (1H, dd, J = 13.4 Hz, J = 6.4 Hz, CH_2Ar), 2.72 (1H, dd, J = 13.4 Hz, J = 7.2 Hz, CH_2Ar); EIMS m/z 371 [M]$^+$ (13), 196 (49), 195 (100), 181 (12), 180 (14), 176 (15), 121 (15), 77 (17); anal. C 64.68; H 5.70; N 3.77%, calcd for $C_{20}H_{21}NO_6$, C 64.52; H 5.62; N 3.73%.

*5-[(6,7-Dimethoxy-1,3-benzodioxol-5-yl)methyl]-3-(4-methoxyphenyl)-4,5-dihydroisoxazole (**2e**):* 19.45 g, 68% yield; white solid; mp 98−100 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.59 (2H, d, J = 8.9 Hz, H-2′,6′), 6.99 (2H, d, J = 8.9 Hz, H-3′,5′), 6.60 (1H, s, H-4″), 5.96 (2H, s, CH_2O), 4.83 (1H, m, H-5), 3.92 (3H, s, OCH_3-6″), 3.79 (3H, s, OCH_3-4′), 3.69 (3H, s, OCH_3-7″), 3.38 (1H, dd, J = 16.8 Hz, J = 10.2 Hz, H-4), 3.08 (1H, dd, J = 16.8 Hz, J = 7.5 Hz, H-4), 2.90 (1H, dd, J = 13.6 Hz, J = 6.8 Hz, CH_2Ar), 2.73 (1H, dd, J = 13.6 Hz, J = 6.8 Hz, CH_2Ar); EIMS m/z 371 [M]$^+$ (26), 196 (37), 195 (100), 181 (15), 180 (21), 176 (15), 121 (11), 77 (13); anal. C 64.68; H 5.70; N 3.77%, calcd for $C_{20}H_{21}NO_6$, C 64.54; H 5.65; N 3.86%.

*3-(4-Methoxyphenyl)-5-(2,3,4,5-tetramethoxybenzyl)-4,5-dihydroisoxazole (**2f**):* 23.57 g, 79% yield; white solid; mp 107−109 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.59 (2H, d, J = 8.8 Hz, H-2′,6′), 6.99 (2H, d, J = 8.8 Hz, H-3′,5′), 6.73 (1H, s, H-6″), 4.89 (1H, m, H-5), 3.80 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.76 (3H, s, OCH_3-4′), 3.73 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.41 (1H, dd, J = 16.9 Hz, J = 10.2 Hz, H-4), 3.11 (1H, dd, J = 16.9 Hz, J = 7.3 Hz, H-4), 2.92 (1H, dd, J = 13.6 Hz, J = 6.7 Hz, CH_2Ar), 2.77 (1H, dd, J = 13.6 Hz, J = 6.7 Hz, CH_2Ar); EIMS m/z 387 [M]$^+$ (15), 212 (70), 211 (100), 197 (37), 196 (55), 181 (24), 176 (57), 166 (16), 153 (19), 151 (16), 148 (14), 121 (47), 92 (31), 91 (21), 77 (61); anal. C 65.10; H 6.50; N 3.62%, calcd for $C_{19}H_{19}NO_5$, C 65.04; H 6.48; N 3.67%.

5-[(1,3-Benzodioxol-5-yl)methyl]-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazole (2bx). Starting 3,4,5-trimethoxybenzonitrile oxide was synthesized in situ according to a literature procedure.[28] A suspension of 3,4,5-trimethoxybenzaldehyde oxime (2.11 g, 10 mmol), safrole 1.94 g (12 mmol), and chloroamine-T (3.1 g, 11 mmol) in 50 mL of EtOH was boiled for 6 h and evaporated under vacuum. The resulting dihydroisoxazole **2bx** was separated by column chromatography (R_f = 0.6, EtOAc−hexane, 1:3): 1.23 g, 33% yield;

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white solid; mp 124−126 °C (EtOAc−hexane, 1:3); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.92 (2H, s, H-2′,6′), 6.91 (1H, s, H-4″), 6.85 (1H, d, J = 7.9 Hz, H-7″), 6.76 (1H, d, J = 7.9 Hz, H-6″), 5.98 (2H, s, OCH_2O), 4.89 (1H, m, H-5), 3.80 (6H, 2s, OCH_3-3′,5′), 3.69 (3H, s, OCH_3-4′), 3.42 (1H, dd, J = 17.0 Hz, J = 10.3 Hz, H-4), 3.08 (1H, dd, J = 17.0 Hz, J = 8.0 Hz, H-4), 2.92 (1H, dd, J = 13.8 Hz, J = 6.4 Hz, CH_2Ar), 2.79 (1H, dd, J = 13.8 Hz, J = 6.8 Hz, CH_2Ar); EIMS m/z 371 $[M]^+$ (13), 236 (20), 235 (16), 181 (15), 136 (20), 135 (100), 79 (11), 77 (33); anal. C 64.68; H 5.70; N 3.77%, calcd for $C_{20}H_{21}NO_6$, C 64.59; H 5.66; N 3.82%.

General Procedure for the Synthesis of Hydroxyketones 3a−f. A solution of isoxazoline **2a−f** (13.5 mmol) and H_3BO_3 (3.34 g, 54 mmol) in 130 mL of MeOH−H_2O (3:1) was stirred under H_2 at 1 atm for 24 h in the presence of Raney Ni (2 g). An additional amount of Raney Ni (2 g) was added and stirred for an additional 24 h under TLC control. The catalyst was removed by filtering through Celite, and MeOH was evaporated from the filtrate in vacuo and extracted by EtOAc. The extract was washed with saturated $NaHCO_3$ to remove traces of amino alcohols **4**, dried by Na_2SO_4, and evaporated to afford target hydroxy ketones **3**. Pure products were obtained by crystallization from hexane−EtOAc or by column chromatography.

*4-(4-Methoxyphenyl-1-yl)-3-hydroxy-1-(4-methoxyphenyl)-1-butanone (**3a**):* 3 g, 74% yield, white solid; mp 91−92 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.89 (2H, d, J = 8.9 Hz, H-2′,6′), 7.14 (2H, d, J = 8.6 Hz, H-2″,6″), 7.02 (2H, d, J = 8.9 Hz, H-3′,5′), 6.84 (2H, d, J = 8.6 Hz, H-3″,5″), 4.73 (1H, d, J = 5.6 Hz, OH), 4.18 (1H, m, H-3), 3.82 (3H, s, OCH_3-4′), 3.72 (3H, s, OCH_3-4″), 3.06 (1H, dd, J = 15.4 Hz, J = 6.0 Hz, CH_2−2), 2.83 (1H, dd, J = 15.4 Hz, J = 4.4 Hz, CH_2−2), 2.69 (2H, d, J = 6.3 Hz, CH_2-4); EIMS m/z 300 $[M]^+$ (1), 282 (15), 150 (40), 136 (9), 135 (100), 134 (10), 121 (50), 107 (9), 92 (16), 78 (16), 77 (30); anal. C 71.98; H 6.71%, calcd for $C_{18}H_{20}O_4$, C 71.92; H 6.68%.

*4-(1,3-Benzodioxol-5-yl)-3-hydroxy-1-(4-methoxyphenyl)-1-butanone (**3b**):* 3.06 g, 72% yield, white solid; mp 69−71 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.90 (2H, d, J = 8.9 Hz, H-2′,6′), 7.02 (2H, d, J = 8.9 Hz, H-3′,5′), 6.81 (1H, d, J = 1.6 Hz, H-4″), 6.80 (1H, d, J = 7.9 Hz, H-7″), 6.67 (1H, dd, J = 7.9 Hz, J = 1.6 Hz, H-6″), 5.95 (2H, s, OCH_2O), 4.74 (1H, d, J = 5.6 Hz, OH), 4.17 (1H, m, H-3), 3.84 (3H, s, OCH_3-4′), 3.06 (1H, dd, J = 15.4 Hz, J = 8.0 Hz, CH_2-2), 2.84 (1H, dd, J = 15.4 Hz, J = 4.4 Hz, CH_2-2), 2.67 (2H, d, J = 6.2 Hz, CH_2-4); EIMS m/z 314 $[M]^+$ (2), 297 (20), 296 (100), 164 (31), 136 (20), 135 (91), 107 (10), 92 (14), 77 (45); anal. C 68.78; H 5.77%, calcd for $C_{18}H_{18}O_5$, C 68.72; H 5.74%.

*(1,3-Benzodioxol-5-yl)-3-hydroxy-1-(3,4,5-trimethoxyphenyl)-1-butanone (**3bx**):* 2.83 g, 56% yield; yellowish oil; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.20 (2H, s, H-2′,6′), 6.83 (1H, c, H-4″), 6.81 (1H, d, J = 7.8 Hz, H-7″), 6.69 (1H, d, J = 7.8 Hz, H-6″), 5.96 (2H, s, OCH_2O), 4.80 (1H, s, OH), 4.19 (1H, m, H-3), 3.83 (6H, s, OCH_3-3′,5′), 3.74 (3H, s, OCH_3-4′), 3.07 (1H, dd, J = 15.4 Hz, J = 7.9 Hz, CH_2-2), 2.95 (1H, dd, J = 15.4 Hz, J = 4.4 Hz, CH_2-2), 2.69 (2H, d, J = 6.3 Hz, CH_2-4); EIMS m/z 357 (3), 356 (16), 239 (4), 210 (13), 196 (11), 195 (100), 164 (13), 152 (7), 136 (8), 135 (46), 122 (5), 109 (8), 92 (3), 77 (28); anal. C 64.16; H 5.92%, calcd for $C_{20}H_{22}O_7$, C 64.04; H 5.86%.

*3-Hydroxy-4-(7-methoxy-1,3-benzodioxol-5-yl)-1-(4-methoxyphenyl)-1-butanone (**3c**):* 3.21 g, 69% yield; yellowish oil; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.90 (2H, d, J = 8.9 Hz, H-2′,6′), 7.02 (2H, d, J = 8.9 Hz, H-3′,5′), 6.47 (2H, s, H-4″,6″), 5.93 (2H, m, OCH_2O), 4.74 (1H, d, J = 5.6 Hz, OH), 4.20 (1H, m, H-3), 3.84 (3H, s, OCH_3-7″), 3.78 (3H, s, OCH_3-4′), 3.06 (1H, dd, J = 15.4 Hz, J = 8.0 Hz, CH_2-2), 2.86 (1H, dd, J = 15.4 Hz, J = 4.4 Hz, CH_2-2), 2.67 (2H, d, J = 6.3 Hz, CH_2-4); EIMS m/z 344 $[M]^+$ (2), 194 (13), 178 (5), 165 (33), 150 (15), 136 (11), 135 (100), 107 (13), 92 (26), 77 (53); anal. C 66.27; H 5.85%, calcd for $C_{19}H_{20}O_6$, C 66.22; H 5.84%.

*4-(4,7-Dimethoxy-1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-methoxyphenyl)-1-butanone (**3d**):* 3.94 g, 78% yield; white solid, mp 65−67 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.88 (2H, d, J = 8.8 Hz, H-2′,6′), 7.02 (2H, d, J = 8.8 Hz, H-3′,5′), 6.46 (1H, s, H-6″), 5.96 (1H, s, OCH_2O), 5.95 (1H, s, OCH_2O), 4.73 (1H, d, J = 5.6 Hz, OH), 4.21 (1H, m, H-3), 3.83 (3H, s, OCH_3-4′), 3.76 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.07 (1H, dd, J = 15.2 Hz, J = 8.1 Hz, CH_2-2), 2.82 (1H, dd, J = 11.0 Hz, J = 4.2 Hz, CH_2-2), 2.70 (1H, dd, J = 13.2 Hz, J = 6.8 Hz, CH_2-4), 2.64 (1H, dd, J = 12.2 Hz, J = 6.3 Hz, CH_2-4); EIMS m/z 374 $[M]^+$ (7), 356 (19), 224 (23), 196 (25), 195 (29), 150 (10), 136 (10), 135 (100), 107 (12), 92 (13), 77 (26); anal. C 64.16; H 5.92%, calcd for $C_{20}H_{22}O_7$, C 64.09; H 5.88%.

*4-(6,7-Dimethoxy-1,3-benzodioxol-5-yl)-3-hydroxy-1-(4-methoxyphenyl)-1-butanone (**3e**):* 2.78 g, 55% yield, white-yellow oil; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.90 (2H, d, J = 8.9 Hz, H-2′,6′), 7.03 (2H, d, J = 8.9 Hz, H-3′,5′), 6.51 (1H, c, H-4″), 5.94 (1H, s, OCH_2O), 5.93 (1H, s, OCH_2O), 4.75 (1H, d, J = 5.7 Hz, OH), 4.20 (1H, m, H-3), 3.89 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.09 (1H, dd, J = 15.3 Hz, J = 8.0 Hz, CH_2-2), 2.83 (1H, dd, J = 15.3 Hz, J = 4.4 Hz, CH_2-2), 2.65 (2H, d, J = 6.5 Hz, CH_2-4); EIMS m/z 374 $[M]^+$ (16), 356 (33), 224 (47), 196 (62), 195 (45), 181 (36), 180 (28), 179 (17), 150 (23), 136 (27), 135 (100), 107 (34), 92 (33), 77 (75); anal. C 64.16; H 5.92%, calcd for $C_{20}H_{22}O_7$, C 64.10; H 5.89%.

*4-(2,3,4,5-Tetramethoxyphenyl-1-yl)-3-hydroxy-1-(4-methoxyphenyl)-1-butanone (**3f**):* 3.057 g, 58% yield; white solid; mp 67−69 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.88 (2H, d, J = 8.9 Hz, H-2′,6′), 7.03 (2H, d, J = 8.9 Hz, H-3′,5′), 6.63 (1H, s, H-6″), 4.76 (1H, d, J = 5.7 Hz, OH), 4.26 (1H, m, H-3), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.10 (1H, dd, J = 15.3 Hz, J = 7.8 Hz, CH_2-2), 2.88 (1H, dd, J = 15.3 Hz, J = 4.6 Hz, CH_2-2), 2.70 (2H, dd, J = 6.5 Hz, J = 2.2 Hz, CH_2-4); EIMS m/z 390 $[M]^+$ (9), 372 (11), 237 (7), 212 (24), 211 (22), 197 (13), 196 (13), 181 (7), 179 (6), 151 (5), 150 (8), 136 (12), 135 (100), 107 (7), 92 (8), 77 (15); anal. C 64.60; H 6.71%, calcd for $C_{21}H_{26}O_7$, C 64.48; H 6.67%.

General Procedure for the Synthesis of 1-Arylnaphthalenes 5b−f. Anhydrous $FeCl_3$ (10−15 mg) was added to the solution of hydroxyketones **3b−f** in Ac_2O (3 mL) and stirred at room temperature for 30 min. The reaction mixture was diluted with water (5 mL), neutralized with $NaHCO_3$, and extracted by CH_2Cl_2 (2 × 15 mL). The extract was washed with brine (2 × 10 mL) and water (10 mL), dried, and then evaporated in vacuo to afford the target arylnaphthalenes **5b−f**. The products were purified by crystallization from AcOEt−hexane or by column chromatography from CH_2Cl_2 extract (EtOAc−hexane, 1:6).

*5-(4-Methoxyphenyl)naphtho[2,3-d][1,3]dioxole (**5b**):* 2.36 g, 18.7% yield; white-yellow solid; mp 104−106 °C (EtOAc−hexane, 1:1) (lit.[16] mp 108−109 °C); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.74 (1H, d, J = 8.1 Hz, H-8), 7.39 (1H, s, H-9), 7.37 (1H, t, J = 7.4 Hz, H-7), 7.36 (2H, d, J = 8.7 Hz, H-2′,6′), 7.21 (1H, dd, J = 7.1 Hz, J = 1.2 Hz, H-6), 7.08 (2H, d, J = 8.7 Hz, H-3′,5′), 7.04 (1H, s, H-4), 6.11 (2H, s, OCH_2O), 3.83 (3H, s, OCH_3-4′); ^{13}C NMR (DMSO-d_6, 125.8 MHz) δ 55.2, 101.2, 101.3, 104.1, 114.0, 124.1, 125.5, 126.5, 128.1, 130.7, 130.7, 132.7, 138.5, 147.14, 147.7, 158.6 (lit.[18]); EIMS m/z 279 $[M + H]^+$ (18), 278 $[M]^+$ (100), 264 (7), 263 (41), 205 (25), 189 (11), 177 (32), 176 (47), 151 (20), 150 (13), 139 (10), 124 (18), 88 (36); anal. C 77.68; H 5.07%, calcd for $C_{18}H_{14}O_3$, C 77.74; H 5.10%.

*5-(3,4,5-Trimethoxyphenyl)naphtho[2,3-d][1,3]dioxole (**5bx**):* 4.21 g, 56.2% yield; white-yellow solid; mp 173−175 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.75 (1H, d, J = 7.9 Hz, H-8), 7.39 (1H, s, H-9), 7.37 (1H, t, J = 7.9 Hz, H-7), 7.27 (1H, d, J = 7.0 Hz, H-6), 7.11 (1H, s, H-4), 6.69 (2H, s, H-2′,6′), 6.12 (2H, s, OCH_2O), 3.83 (6H, s, 2OCH_3-3′,5′), 3.75 (3H, s, OCH_3-4′); ^{13}C NMR (DMSO-d_6, 125.76 MHz) δ 56.84, 61.0, 102.2, 102.2, 104.9, 107.9, 124.7, 126.1, 126.2, 127.5, 128.8, 128.9, 131.5, 137.0, 137.7, 139.8, 148.0, 148.6, 153.7; EIMS m/z 339 $[M + H]^+$ (20), 338 $[M]^+$ (100), 324 (12), 323 (53), 295 (9), 263 (10), 237 (13), 209 (14), 207 (10), 205 (10), 179 (14), 169 (13), 163 (19), 153 (16), 151 (37), 150 (23), 139 (18), 104 (26), 89 (17); anal. C 71.00; H 5.36%, calcd for $C_{20}H_{18}O_5$, C 71.12; H 5.40%.

*4-Methoxy-5-(4-methoxyphenyl)naphtho[2,3-d][1,3]dioxole (**5c**):* 0.23 g, 26% yield; yellowish solid, R_f = 0.5; mp 104−106 °C (EtOAc−hexane, 1:1); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.72 (1H, dd, J = 8.1 Hz, J = 0.9 Hz, H-8), 7.32 (1H, t, J = 7.6 Hz, H-7), 7.20 (2H, d, J = 8.6 Hz, H-2′,6′), 7.18 (1H, s, H-9), 7.03 (1H, dd, J = 7.1 Hz, J = 1.1 Hz, H-6), 6.92 (2H, d, J = 8.6 Hz, H-3′,5′), 6.10 (2H, s, OCH_2O), 3.80

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(3H, s, OCH_3-4′), 3.30 (3H, s, OCH_3-4); ^{13}C NMR (DMSO-d_6, 125.76 MHz) δ 54.9, 59.3, 99.7, 101.4, 112.1, 122.6, 123.8, 126.8, 127.7, 129.4, 131.6, 136.4, 137.2, 137.4, 137.5, 147.9, 157.5; EIMS m/z 309 $[M + H]^+$ (21), 308 $[M]^+$ (100), 294 (6), 293 (31), 263 (16), 262 (30), 235 (38), 220 (17), 205 (10), 192 (42), 176 (36), 165 (17), 164 (42), 163 (63), 135 (18), 125 (15), 117 (17), 116 (15), 97 (20), 88 (29); anal. C 74.01; H 5.23%, calcd for $C_{19}H_{16}O_4$, C 74.06; H 5.27%.

*4-Methoxy-9-(4-methoxyphenyl)naphtho[1,2-d][1,3]dioxole (**5c-iso**):* 0.20 g, 22% yield; yellowish solid; R_f = 0.7; mp 118−120 °C (EtOAc−hexane, 1:1); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.79 (1H, dd, J = 7.7 Hz, J = 1.0 Hz, H-6), 7.33 (1H, dd, J = 8.3 Hz, J = 7.1 Hz, H-7), 7.30 (2H, d, J = 8.6 Hz, H-2′,6′), 7.10 (1H, dd, J = 7.0 Hz, J = 1.0 Hz, H-8), 6.93 (2H, d, J = 8.6 Hz, H-3′,5′), 5.93 (2H, s, OCH_2O), 3.95 (3H, s, OCH_3-4), 3.80 (3H, s, OCH_3-4′); ^{13}C NMR (DMSO-d_6, 125.76 MHz) δ 54.9, 55.8, 101.0, 102.8, 112.5, 113.8, 123.9, 126.4, 126.6, 130.5, 131.0, 133.42, 134.4, 134.9, 141.9, 144.6, 158.2; EIMS m/z 309 $[M + H]^+$ (21), 308 $[M]^+$ (100), 293 (6), 265 (10), 249 (11), 237 (20), 221 (18), 220 (12), 209 (18), 205 (28), 194 (25), 192 (32), 178 (22), 177 (21), 176 (45), 165 (51), 164 (51), 163 (90), 154 (59), 132 (19), 124 (15), 110 (21), 103 (23), 88 (79); anal. C 74.01; H 5.23%, calcd for $C_{19}H_{16}O_4$, C 74.05; H 5.25%.

*4,9-Dimethoxy-5-(4-methoxyphenyl)naphtho[2,3-d][1,3]dioxole (**5d**):* 0.75 g, 89% yield; white solid, R_f = 0.4; mp 89−93 °C (EtOAc−hexane, 1:1); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.98 (1H, dd, J = 8.4 Hz, J = 1.2 Hz, H-8), 7.36 (1H, dd, J = 7.7 Hz, J = 7.1 Hz, H-7), 7.20 (2H, d, J = 8.6 Hz, H-2′,6′), 7.08 (1H, dd, J = 7.1 Hz, J = 1.2 Hz, H-6), 6.91 (2H, d, J = 8.6 Hz, H-3′,5′), 6.12 (2H, s, OCH_2O), 4.04 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.21 (3H, s, OCH_3-4′); ^{13}C NMR (DMSO-d_6, 125.76 MHz) δ 54.9, 59.5, 60.1, 101.8, 112.1, 120.3, 122.7, 123.4, 125.4, 128.4, 129.5, 131.7, 133.0, 135.4, 136.1, 137.2, 138.9, 157.6; EIMS m/z 339 $[M + H]^+$ (21), 338 $[M]^+$ (100), 324 (6), 323 (26), 293 (13), 292 (66), 278 (11), 277 (29), 263 (13), 261 (18), 235 (20), 179 (10), 167 (19), 165 (22), 163 (45), 151 (49), 150 (38), 139 (72), 87 (34); anal. C 71.00; H 5.36%, calcd for $C_{20}H_{18}O_5$, C 71.06; H 5.38%.

*4,5-Dimethoxy-9-(4-methoxyphenyl)naphtho[1,2-d][1,3]dioxole (**5e**):* 3.61 g, 54% yield; white-yellow solid; mp 86−88 °C (EtOAc−hexane, 1:1); ^1H NMR (DMSO-d_6, 500 MHz) δ 7.97 (1H, dd, J = 7.8 Hz, J = 0.7 Hz, H-6), 7.37 (1H, dd, J = 8.6 Hz, J = 7.0 Hz, H-7), 7.30 (2H, d, J = 8.6 Hz, H-2′,6′), 7.16 (1H, dd, J = 7.0 Hz, J = 0.7 Hz, H-8), 6.93 (2H, d, J = 8.6 Hz, H-3′,5′), 5.92 (2H, s, OCH_2O), 4.02 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.80 (3H, s, OCH_3-4′); ^{13}C NMR (DMSO-d_6, 125.76 MHz) δ 55.1, 60.4, 61.7, 101.0, 112.7, 114.0, 121.0, 123.9, 124.5, 127.7, 130.6, 133.4, 135.3, 136.7, 137.0, 138.3, 141.0, 158.4; EIMS m/z 339 $[M + H]^+$ (17), 338 $[M]^+$ (71), 324 (22), 323 (100), 278 (20), 277 (15), 235 (10), 169 (12), 163 (14), 151 (23), 150 (13), 139 (23); anal. C 71.00; H 5.36%, calcd for $C_{20}H_{18}O_5$, C 71.08; H 5.39%.

*1,2,3,4-Tetramethoxy-5-(4-methoxyphenyl)naphthalene (**5f**):* 4.53 g, 62 6% yield; white solid; mp 74−76 °C (EtOAc−hexane, 1:1); ^1H NMR (DMSO-d_6, 500 MHz) δ 8.03 (1H, dd, J = 8.4 Hz, J = 1.2 Hz, H-8), 7.44 (1H, dd, J = 8.4 Hz, J = 7.0 Hz, H-7), 7.22 (2H, d, J = 8.6 Hz, H-2′,6′), 7.14 (1H, dd, J = 7.0 Hz, J = 1.2 Hz, H-6), 6.92 (2H, d, J = 8.6 Hz, H-3′,5′), 3.95 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.10 (3H, s, OCH_3-4′); ^{13}C NMR (DMSO-d_6, 125.76 MHz) δ 55.1, 60.4, 61.1, 61.4, 112.2, 120.8, 123.2, 124.5, 126.1, 129.2, 129.8, 136.2, 137.5, 143.5, 144.1, 145.4, 145.5, 157.7; EIMS m/z 355 $[M + H]^+$ (24), 354 $[M]^+$ (100), 340 (11), 339 (49), 308 (18), 293 (24), 253 (13), 182 (11), 162 (13), 161 (12), 139 (21), 119 (9); anal. C 71.17; H 6.26%, calcd for $C_{21}H_{22}O_5$, C 71.23; H 6.29%.

4-(4,7-Dimethoxy-1,3-benzodioxol-5-yl)-1-(4-methoxyphenyl)-1,3-butanediol (6d). $NaBH_4$ (0.39 g, 10.30 mmol) was added in small portions to a stirred solution of hydroxy ketone **3d** (2.58 g, 6.86 mmol) in MeOH. The mixture was stirred at room temperature for 1 h, diluted with water (200 mL), and extracted by CH_2Cl_2 (5 × 50 mL). The extract was washed by water, dried with Na_2SO_4, and evaporated to afford the target diol **6d**: 2.41 g, 93% yield; yellowish oil; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28 (2H, d, J = 8.7 Hz, H-2′,6′), 6.86 (2H, d, J = 8.7 Hz, H-3′,5′), 6.29 (1H, m, H-6″), 5.95 (2H, m, OCH_2O), 5.02 (0.7H, d, J = 7.4 Hz, OH-3), 4.87 (0.3H, d, J = 7.4 Hz, OH-3), 4.05 (1H, m, H-3), 3.88 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.79 (3H, s, OCH_3-4′), 3.22 (0.3H, s, OH-1), 3.11 (0.7H, s, OH-1), 2.78 (1H, dd, J = 13.8 Hz, J = 5.4 Hz, CH_2-4), 2.74 (1H, m, H-1), 2.70 (1H, dd, J = 13.8 Hz, J = 8.1 Hz, CH_2-4), 1.95 and 1.92 (2H, dd, J = 8.2 Hz, J = 3.1 Hz, CH_2-2), 1.86 and 1.83 (2H, dd, J = 8.6 Hz, J = 3.4 Hz, CH_2-2); EIMS m/z 376 $[M]^+$ (6), 244 (7), 196 (40), 195 (100), 181 (19), 163 (17), 137 (42), 135 (45), 109 (29), 94 (24), 77 (38); anal. C 63.82; H 6.43%, calcd for $C_{20}H_{24}O_7$, C 63.72; H 6.39%.

4,9-Dimethoxy-8-(4-methoxyphenyl)-5,6,7,8-tetrahydronaphtho[2,3-*d*][1,3]dioxol-6-ol (7d). A solution of diol **6d** (0.2 g, 0.53 mmol) and TsOH (0.05 g, 0.29 mmol) in benzene (3 mL) was stirred for 30 min at room temperature, diluted with benzene (20 mL), washed with water (2 × 10 mL), and evaporated in vacuo to afford tetrahydronaphthalene **7d**: 0.18 g, 95% yield; yellowish oil; ^1H NMR (DMSO-d_6, 500 MHz) δ 6.95 and 6.84 (2H, d, J = 8.6 Hz, H-2′,6′), 6.80 (2H, d, J = 8.6 Hz, H-3′,5′), 5.96 (1H, s, OCH_2O), 5.92 (1H, m, OCH_2O), 4.81 (0.6H, s, OH), 4.67 (0.4H, s, OH), 4.31 (1H, dd, J = 5.5 Hz, J = 2.3 Hz, H-8), 4.09 (1H, t, J = 8.9 Hz, H-8), 3.87 (1.2H, s, OCH_3-9), 3.85 (1.8H, s, OCH_3-9), 3.70 (3H, s, OCH_3-4), 3.69 (1H, m, H-6), 3.06 (3H, s, OCH_3-4′), 3.02 and 2.25 (2H, 2m, CH_2-5), 2.25 and 1.39 (1H, 2m, CH_2-7), 1.90 and 1.77 (1H, m, CH_2-7); ^{13}C NMR (DMSO-d_6, 125.76 MHz) δ 33.0, 33.2, 41.0, 43.9, 54.8, 58.0, 58.8, 59.3, 59.4, 61.1, 65.7, 101.0, 113.2, 113.3, 122.0, 122.2, 123.5, 125.2, 127.7, 128.4, 135.4, 135.7, 135.8, 136.5, 136.6, 136.7, 137.2, 138.9, 141.1, 156.9, 157.1; EIMS m/z 359 $[M + H]^+$ (9), 358 $[M]^+$ (43), 340 (7), 325 (5), 309 (12), 251 (11), 250 (13), 221 (11), 219 (93), 209 (10), 195 (23), 181 (11), 170 (19), 165 (16), 163 (11), 155 (16), 152 (18), 139 (22), 133 (27), 128 (19), 127 (20), 121 (100), 115 (34), 108 (25), 91 (32), 77 (41); anal. C 67.03; H 6.19%, calcd for $C_{20}H_{22}O_6$, C 67.12; H 6.23%.

Sea Urchin Embryo Assay.[29] Adult sea urchins, *Paracentrotus lividus* L. (Echinidae), were collected from the Mediterranean Sea on the Cyprus coast and kept in an aerated seawater tank. Gametes were obtained by intracoelomic injection of 0.5 M KCl. Eggs were washed with filtered seawater and fertilized by adding drops of diluted sperm. Embryos were cultured at room temperature under gentle agitation with a motor-driven plastic paddle (60 rpm) in filtered seawater. The embryos were observed with a Biolam light microscope (LOMO, St. Petersburg, Russia). For treatment with the test compounds, 5 mL aliquots of embryo suspension were transferred to six-well plates and incubated as a monolayer at a concentration up to 2000 embryos/mL. Stock solutions of compounds were prepared in DMSO at a 10 mM concentration followed by a 10-fold dilution with 96% EtOH. This procedure enhanced the solubility of the test compounds in the salt-containing medium (seawater), as evidenced by microscopic examination of the samples. The maximal tolerated concentrations of DMSO and EtOH in the in vivo assay were determined to be 0.05% and 1%, respectively. Higher concentrations of either DMSO (≥0.1%) or EtOH (>1%) caused nonspecific alteration and retardation of the sea urchin embryo development independent of the treatment stage. The antiproliferative activity was assessed by exposing fertilized eggs (8−20 min after fertilization, 45−55 min before the first mitotic cycle completion) to 2-fold decreasing concentrations of the compound. Podophyllotoxin (Sigma-Aldrich) served as a positive control. Cleavage alteration was clearly detected at 2.5−5.5 h after fertilization. The effects were estimated quantitatively as an effective threshold concentration, resulting in cleavage alteration. At these concentrations, all tested molecules caused 100% cleavage alteration and embryo death before hatching, whereas at 2-fold lower concentrations the compounds failed to produce any effect.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Experimental procedures for compounds **3d**, **4d**, **6c**, and **6d**; ^{1}H NMR and ^{13}C NMR spectra of compounds **2**–**7** (PDF)

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Notes

The authors declare no competing financial interest.

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