New syntheses of dillapiol [4,5-dimethoxy-6-(2-propenyl)-1,3-benzodioxole], its 4-methylthio and other analogs

Sherry L. Majerus, Najma Alibhai, Sasmita Tripathy, and Tony Durst

Abstract: Three syntheses of the natural synergist dillapiol from the natural, commercially available sesamol as starting material, are described. A major difference between these is the order of introduction of the additional methoxy and allyl substituents. In one of the syntheses, a formyl group is introduced at C4 via an electrophilic aromatic substitution reaction and then converted into the methoxy group using a Baeyer–Villiger reaction and subsequent methylation; in the other two, a directed ortho-metalation, Baeyer–Villiger, methylation sequence was employed. Various intermediates along the synthetic route were used to generate more than 30 analogs, including the 4-thiomethyldillapiol, to investigate the structure activity relationships of the pesticide synergism of these compounds. Radio-labeled dillapiol, bearing ^{14}C at the C4 methoxy group was also prepared. Initial screening with mosquito larvae showed that most of the derivatives prepared in this study had signifacant synergistic activities in combination with the phototoxic larvicide α-therthiophene.

Key words: dillapiol, insecticide synergists, dillapiol analogs, 4-methylthiodillapiol.

Résumé : On décrit trois synthèses du dillapiol, un produit naturel de synergie, qui ont été réalisées à partir du sésamol, un produit naturel disponible commercialement. Ces trois ces synthèses diffèrent principalement par l'ordre d'introduction des substituants méthoxy et alkyles additionnels. Dans l'une de ces synthèses, le groupe formyle est introduit en C-4 par le biais d'une réaction de substitution aromatique électrophile et elle est ensuite transformée en groupe méthoxy à l'aide d'une réaction de Baeyer–Villiger et une réaction de méthylation subséquente; dans les deux autres, on fait appel à la séquence de réaction impliquant une métalation ortho dirigée, une réaction de Baeyer–Villiger et une méthylation. On a utilisé divers intermédiaires obtenus au cours de ces voies de synthèses pour générer plus de 30 analogues, y compris le 4-thiométhyldillapiol, afin d'en étudier les relations structure-activité de synergie de ces composés comme pesticide. On a aussi préparé du dillapiol radioactivement marqué par du ^{14}C dans le groupe méthoxy en C-4. Des évaluations initiales avec des larves de moustiques montrent que la plupart des dérivés préparés au cours de cette étude présentent des activités importantes de synergie lorsqu'on les utilise en combinaison avec l'α-therthiophéne, un larvicide phototoxique.

Mots clés : dillapiol, effet de synergie pour les insecticides, analogues de dillapiol, 4-méthylthiodillapiol.

Introduction

During the past few years we have been involved in a project aimed at developing natural insecticides (1). Part of this includes the use of the naturally occurring synergist dillapiol (**1**). Dillapiol is a member of a group of both natural and synthetic synergists known as polysubstrate mono-oxygenase inhibitors (PMSO) whose key structural unit is a benzene ring bearing a methylenedioxy unit (2). This unit binds strongly to the heme portion of the cytochrome P-450 thereby inhibiting the oxidation of various other substrate such as insecticides and delaying their rate of elimination from the insects. Examples of natural lignans with known synergistic activity, in addition to the dillapiol, are myristicin (**2**), safrole (**3**), and sessamin (**4**). Piperonyl butoxide (**5**) the commonly used commercial synergist for pyrethroids and carbamates, is also known to inhibit PSMOs.

Dillapiol is a monolignan and a major constituent of the essential oils of a number of plants, including Indian dill (*Antheum graveolus*) (3), and *Piper aduncum*, (4), a species in the Piperaceae family. The latter grows as a small shrub in many tropical areas such as Central America, the West Indies, and Southeast Asia. The development of dillapiol for commercial purposes requires either an inexpensive reliable natural source or a viable synthetic source. Additionally for registration purposes both the toxicity to nontarget species and pharmacokinetics including the nature of the metabolites need to be known. The latter studies can be carried out best with isotopically labeled material.

Three syntheses of dillapiol have previously been reported. 3,4,5-Tri-methoxyacetophenone (**5**), 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin) (**6**), and 1,2,3-trimethoxybenzene (**7**) were used as starting materials. These syntheses required

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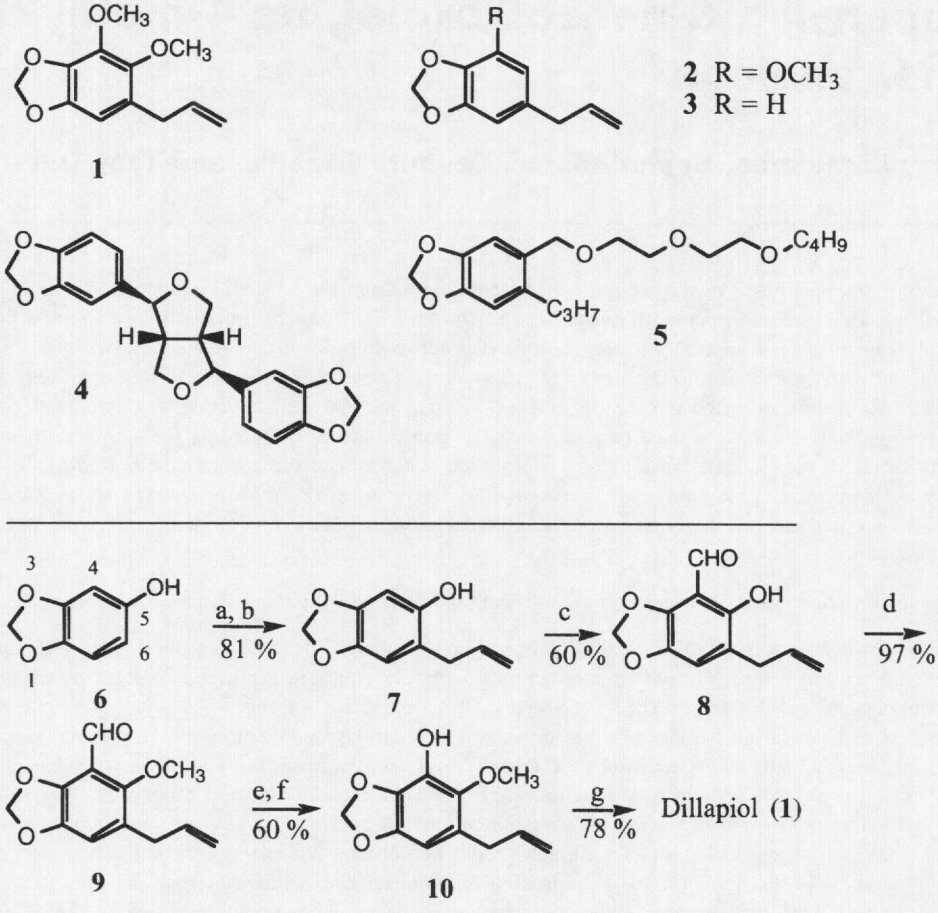
Scheme 1. Reagents: (*a*) K_2CO_3–CH_2=$CHCH_2Br$; (*b*) *N*,*N*-dimethylaniline (180°C); (*c*) $(CH_2O)n$–$SnCl_4$–Bu_3N; (*d*) CH_3I–K_2CO_3; (*e*) MCPBA–$CHCl_3$ (18 h, 0°C); (*f*) LiOH–THF–H_2O; (*g*) CH_3I–K_2CO_3–acetone.



5–7 steps and occurred in 2, 10, and 6% yield, respectively. None of the three syntheses is efficient or amenable to the introduction of isotopic carbon in the form of the relative inexpensive methyl iodide. We therefore decided to investigate several new syntheses which would be not only more efficient and enable us to introduce the labeled CH_3I in the last synthetic step, but also enable us to generate a family of derivatives to initiate a structure–activity relationship study. Finally, access to various intermediates is expected to help in the identification of metabolites.

Discussion of results

Three syntheses have been completed starting with sesamol (**6**). These are shown in Schemes 1–3. The structure of the intermediates generated in each sequence were determined mainly by ^1H NMR. The assignments were supported by ^{13}C NMR, IR, and HRMS data. These are given in the experimental section.

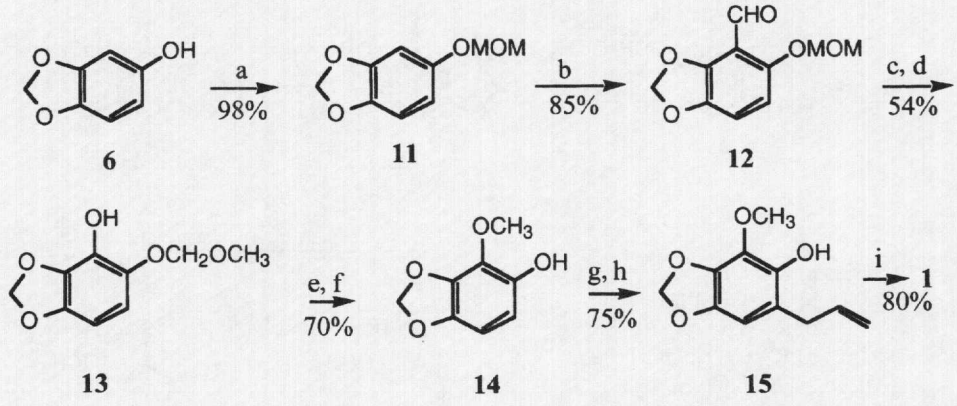
In the first synthesis, Scheme 1, sesamol (**6**)[2] was converted to the *ortho*-allylated phenol **7** in 81% overall yield via *O*-allylation, followed by a Claisen rearrangement. Introduction of the formyl group into the 4 position in **7** was accomplished by treatment with formaldehyde, $SnCl_4$, and tributylamine (8) to afford **8** in 60% isolated yield. Replacement of tributylamine by other tertiary amines such as triethyl- or trioctylamine either reduces or did not improve the yield of **8**. The variation of other reaction parameters such as temperature and reaction time also did not result in yield improvements.

This compound was quantitatively methylated to **9** in preparation for the Baeyer–Villiger and subsequent hydrolysis of the formate ester to form **10**. The conversion of **9** to **10** was carried out using 1 equiv. of MCPBA in $CHCl_3$ at 0°C for 18 h and afforded the formyl intermediate in 71% isolated yield, saponification of which gave **10.** Under these conditions competition by the alkene moiety for the peracid to give an epoxide was minor; at room temperature the rates of desired Baeyer–Villiger and the epoxidation were quite comparable. Finally, methylation of **10** with CH_3I–K_2CO_3 in acetone afforded pure dillapiol. Replacement of cold methyl iodide with carbon-14 labeled material afforded radiolabeled dillapiol, suitable for metabolism studies.

The overall yield of dillapiol from sesamol via Scheme 1, based on the isolated yields of each intermediate, is more than 21%. The major shortcomings of this route are the rather stringent conditions required for the introduction of the formyl group and the problem of the competing

[2] The numbering used throughout this paper is based on the IUPAC numbering of the 1,3-benzodioxole ring system. See structure **6**, Scheme 1.

Scheme 2. Reagents: (*a*) MOM-Cl–*n*BuLi; (*b*) *n*BuLi, THF, (–78°C), then DMF; (*c*) MCPBA; (*d*) 10% KOH; (*e*) K_2CO_3 and CH_3I; (*f*) CH_3CO_2H, NaI; (*g*) K_2CO_3, CH_2=$CHCH_2Br$; (*h*) *N*,*N*-dimethylaniline (180°C); (*i*) K_2CO_3 and CH_3I.



epoxidation of the terminal double bond during the Baeyer–Villiger reaction of **9**. These difficulties became more severe on attempted scale-up.

Considerable effort was expended to avoid the sensitive reactions and shorten the synthesis by going directly from **7** to the resorcinol **20** and hence to dillapiol. Direct *o*-hydroxylation of **7** using H_2O_2–$AlCl_3$ according to Kurz and Johnson (9) or by use of oxygen and copper metal in the presence of $CuCl_2$ as developed by Capdevielle and Maumy (10) was unsuccessful and gave mainly recovered **7**.

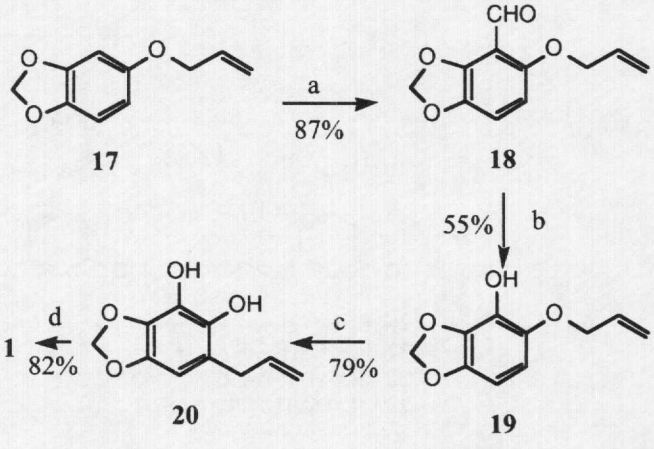
In the second synthesis, Scheme 2, the MOM-protected sesamol **11** was *o*-metallated (11) and treated with DMF to produce the aldehyde **12** in 85% yield. The protection of phenol as a THP derivative, thus avoiding the rather expensive MOM-chloride, was not possible since reaction of **6** with dihydopyran in the presence of acid resulted in the introduction of the THP unit at C6 via an electrophile aromatic substitution to afford **16** rather than the desired phenol protection.

Baeyer–Villiger oxidation followed by basic hydrolysis afforded phenol **13** which was methylated to give **14**. Removal of the MOM group set the stage for alkylation and subsequent Claisen rearrangement to afford phenol **15**, methylation of which gave dillapiol **1**. The overall yield of dillapiol via Scheme 2 was 19%.

After this synthesis was completed we realized that one might be able to avoid the protection–deprotection sequence if *ortho*-directed metallation and subsequent introduction of the formyl group could be carried out on the allyl ether **17** to give **18**. The conversion of **18** to dillapiol would require first a Baeyer–Villiger reaction and hydrolysis to the resorcinol **19** and then double methylation to dillapiol. Such a sequence would save three steps from the synthesis shown in Scheme 2.

We were concerned that **17** would undergo a 1,2-Wittig rearrangement rather than the directed *ortho*-metallation. Fortunately, this fear was unfounded and reaction of **17** with 1 equiv. of *n*Buli followed addition of DMF gave **18** in 87% isolated yield. Conversion to **19** was successful upon stirring with MCPBA at 0°C for 24 h. The reduced nucleophilicity of the double bond in **18** relative to **9** allows the Baeyer–Villiger reaction to proceed without competition from the epoxidation of the allyl ether. The intermediate formate ester was hydrolyzed to **19** without purification. Claisen rearrangement of **19** at 190°C afforded the resorcinol **20** which was methylated to dillapiol. The overall yield of dillaiol from sesamol via Scheme 3 is 31%.

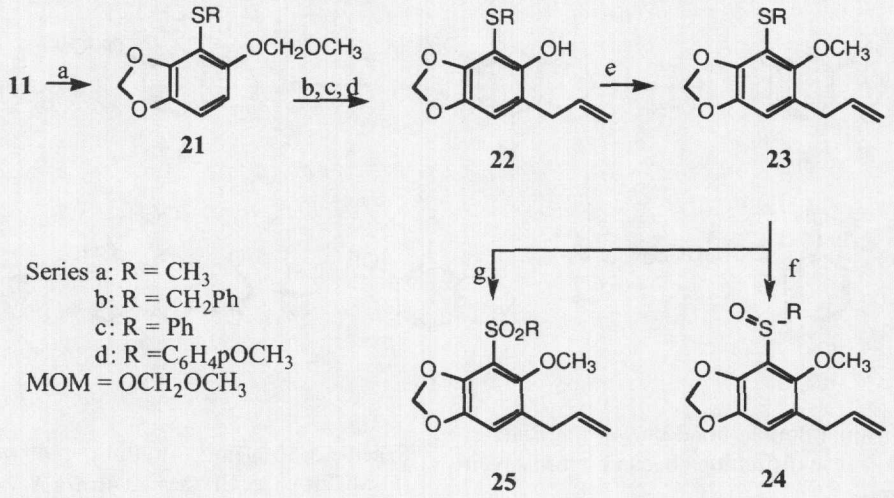
Scheme 3. Reagents: (*a*) *n*BuLi, THF, (–78°C), then DMF; (*b*) MCPBA (25°C), then KOH; (*c*) *N*,*N*-dimethylaniline (180°C); (*d*) CH_3I, K_2CO_3, acetone.

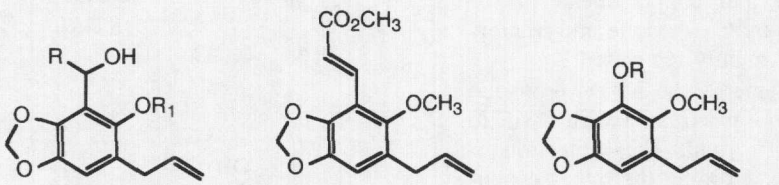


Synthesis of dillapiol analogues

Several of the intermediates in Schemes 1 and 2 were suitable for the preparation of dillapiol analogues. These compounds have been evaluated for their ability to synergize the insecticidal property of α-terthienyl when determined in the presence of light (12). For example, *ortho*-metalation of the MOM-protected sesamol **11**, followed by treatment with dimethyl disulfide afforded the *S*-methyl derivative **21** in 91% yield. This compound was converted via **22a** into the 3-thiomethyl analog of dillapiol **23a** in four steps in 48% overall yield. Oxidation afforded the sulfoxide and sulfone analogs **24a** and **25a**, respectively (Scheme 4). A number of other sulfide, sulfoxide, and sulfone analogs were also prepared in a similar manner simply by replacing dimethyl disulfide with other disulfides (Scheme 4). Surprisingly, reaction of the *ortho*-lithiated allyl ether with dimethyl disulfide was not nearly as efficient as reaction with DMF and afforded only about 55% of the desired product. In addition, a significant amount of a by-product which was difficult to separate from the desired product was obtained. The

Scheme 4. Reagents: (*a*) *n*BuLi, THF, (–78°C), then RSSR; (*b*) Hcl–MeOH–NaI; (*c*) allyl bromide – K_2CO_3 – acetone; (*d*) *N*,*N*-dimethylaniline (180°C); (*e*) CH_3I–K_2CO_3–acetone; (*f*) MCPBA (1.1 equiv.); (*g*) MCPBA (2.2 equiv.).





26 R,R_1 = H
27 R = C_8H_{17}, R_1 = H
28 R = H, R_1 = OCH_3
29 R = C_8H_{17}, R_1 = OCH_3

30

31 R = C_8H_{17}

by-product has not been identified and this route to sulfur analogues of dillapiol was not pursued further.

The aldehydes **8** and **9** served as a source of a number of derivatives. Thus, reduction of **8** with $NaBH_4$, or reaction with *n*-octylmagnesium iodide, gave the derivatives **26** and **27**, respectively.

Similarly, the methoxyaldehyde **9** was reduced to **28**, or converted to **29** upon addition of *n*-octylmagnesium bromide. Reaction of **9** with methyl (triphenylphosphoranylidene) acetate resulted in formation of the unsaturated ester **30**. The ^{1}H NMR of both **27** and **29** show nonequivalence of each of the methylene hydrogens both α and β to the chiral benzylic center. The β methylene hydrogen nonequivalence is somewhat surprising and may be due to a combination of both steric crowding and intramolecular hydrogen bonding resulting in a preferred conformation in which each of these sets of geminal hydrogens continue to show nonequivalence.

The use of the phenol **10** allowed us to generate ethers such as **31** and thereby test how increased lipophilicity relative to dillapiol affects the synergism of these compounds.

Biological results

Detailed SAR studies of the compounds described in this paper and a number of other analogs as synergists for the light α-terthienyl (α-T) is being published elsewhere (12). Qualitatively, only a few derivatives showed activity comparable to or greater than dillapiol. The most active derivative was the cinnamate ester **30** with a synergism factor 30% higher than dillapiol. In the sulfur series the sulfides showed synergism effects of approximately 1.1–1.3, relative to dillapiol equals. In contrast the corresponding sulfoxides and sulfones had effects which were approximately 40–60% of that observed for dillapiol.

Experimental

General comments

Unless stated otherwise, ^{1}H NMR were obtained at 200 or 500 MHz, and ^{13}C NMR spectra at 125 MHz. Solvents used in reactions were distilled prior to use. BuLi was purchased from Aldrich as a hexane solution and titrated [diphenylacetic acid] prior to use. Usual work-up refers to partitioning of the reaction mixture between an organic solvent such as ether, ethyl acetate, or dichloromethane and water or 5% NH_4Cl solution, drying of the organic phase with anhydrous $MgSO_4$, and evaporating the solvents at reduced pressure. Yields, unless indicated otherwise, refer to chromatograpically pure fractions.

5-Hydroxy-6-(2-propenyl)-1,3-benzodioxole (7)

This compound was prepared in 81% overall yield following the procedure of Grubbs et al. (13). Melting point 74–76°C, lit. (13) mp 74–76°C.

4-Formyl-5-hydroxy-6-(2-propenyl)-1,3-benzodioxole (8)

Paraformaldehyde (0.56 g, 18.5 mmol) was added to toluene (5.6 mL) containing 1.5 g (8.4 mmol) of **7**, 0.1 mL (0.84 mmol) of tin tetrachloride, and 0.8 mL (3.37 mmol) of tri-*n*-butylamine. The resulting yellow solution was heated 8 h at 100°C, then cooled, acidified with 2 N HCl to pH 2, and extracted with ether. Purification by silica gel chromatography (1:1, hexane :CH_2Cl_2) afforded 1.05 g (60%) of **8** as a bright yellow solid, mp 68–70°C. IR (cm^{-1}): 1658, 3215. ^1H NMR δ: 3.27–3.29 (m, 2H), 5.03–5.07 (m, 2H), 5.86–5.94 (m, 1H), 6.00 (s, 2H), 6.87 (s, 1H), 10.09 (s, 1H), 10.65 (s, 1H). ^{13}C NMR δ: 32.8, 102.5, 106.7, 116.0, 117.6, 119.0, 136.1, 140.1, 148.5, 152.3, 191.3. HRMS calcd. for $C_{11}H_{10}O_4$: 206.0579; found: 206.0568.

4-Formyl-5-methoxy-6-(2-propenyl)-1,3-benzodioxole (9)

Potassium carbonate (1.31 g, 9.45 mmol) and methyl iodide (3.92 mL, 63.0 mmol) were added sequentially to a solution of aldehyde **8** (1.30 g, 6.30 mmol) in acetone (10 mL). The resulting solution was allowed to stir at rt for 48 h, after which time the solvent was evaporated under reduced pressure. The remaining K_2CO_3 was dissolved in water and the aqueous phase extracted with ether (3 × 15 mL). Chromatography (5:1, hexane:EtOAc) of the crude product gave 1.35 g (97%) of **9** as a pale yellow solid, mp 101–102°C. ^1H NMR δ: 3.32 (dt, 2H, *J* = 6.4, 1.5 Hz), 3.77 (s, 3H), 5.03–5.08 (m, 2H), 5.86–5.91 (m, 1H), 6.05 (s, 2H), 6.83 (s, 1H), 10.23 (s, 1H). ^{13}C NMR δ: 33.0, 64.1, 102.9, 114.2, 114.7, 116.4, 125.7, 136.5, 144.9, 146.9, 153.6, 188.1. IR (cm^{-1}): 1689. HRMS calcd. for $C_{12}H_{12}O_4$: 220.0736; found: 220.0754.

4-Hydroxy-5-methoxy-6-(2-propenyl)-1,3-benzodioxole (10)

To a cooled (0°C) solution of aldehyde **9** (210 mg, 0.95 mmol) in dry $CHCl_3$ (6 mL) was added in one portion MCPBA (0.30 g, 0.95 mmol, 55%). After 18 h, the reaction mixture was allowed to reach rt and washed with sodium sulfite (sat., 2 × 10 mL), sodium bicarbonate (sat., 1 × 10 mL), and water (1 × 10 mL). The extract was dried over Na_2SO_4, filtered and evaporated to dryness. The resulting oily residue was purified by flash chromatography (3:1, Hex:EtOAc) to give the formyl derivative of **10** as a colorless oil (160 mg, 71%). IR (cm^{-1}): 1759. ^1H NMR δ: 3.32 (d, 2H, *J* = 6.5 Hz), 3.69 (s, 3H), 5.03–5.06 (m, 2H), 5.86–5.93 (m, 1H), 5.94 (s, 2H), 6.56 (s, 1H), 8.26 (s, 1H). ^{13}C NMR δ: 33.6, 61.8, 102.3, 107.0, 116.1, 126.3, 126.8, 136.8, 144.6, 144.8, 157.9. HRMS calcd. for $C_{12}H_{12}O_5$: 236.0685; found: 236.0690.

To a solution of the above formyl derivative (250 mg, 1.06 mmol) in THF (9 mL) was added 1 mL of a 3 N NaOH solution. The resulting homogeneous solution was stirred at rt for 1 h and diluted with brine. Usual work-up gave **10** (180 mg, 82%) as a pale yellow solid, mp 61–63°C. IR (cm^{-1}): 3523. ^1H NMR δ: 3.31 (dt, 2H, *J* = 6.5, 1.4 Hz), 3.73 (s, 3H), 5.03–5.07 (m, 2H), 5.50 (s, 1H), 5.87–5.93 (m, 1H), 5.90 (s, 2H), 6.25 (s, 1H). ^{13}C NMR δ: 33.6, 61.8, 101.0, 101.7, 115.9, 125.2, 132.7, 133.5, 137.0, 141.1, 144.9. HRMS calcd. for $C_{11}H_{12}O_4$: 208.0736; found: 208.0740.

4,5-Dimethoxy-6-(2-propenyl)-1,3-benzodioxole)(dillapiol) (1)

A mixture of **10** (100 mg, 0.48 mmol), CH_3I (0.28 mL), and K_2CO_3 (0.1 g) was stirred at rt for 72 h. The solvent was evaporated. Usual work-up afforded, after chromatography (5:1, hexane:EtOAc), 80 mg (78%) of dillapiol. The physical and spectroscopic properties were identical to those of the commercial material.

5-(Methoxymethoxy)-1,3-benzodioxole (11)

To a solution of sesamol (5.0 g, 36.2 mmol) in 20 mL of dry THF at 0°C was added 1 equiv. of BuLi (16.5 mL, 2.2 M). The reaction mixture was stirred for 30 min and then 1.5 equiv. of chloromethyl methyl ether (4.4 g, 4.1 mL) was added. The resulting mixture was stirred at rt for 24 h and then quenched with 10 mL of saturated NH_4Cl. The usual work-up gave 6.5 g (98%) of **11** as a colorless liquid. The product was used as such. EI–MS (*m/z*, %): 182 ($M^{+\cdot}$, 100), 152 (75), 137 (30). ^1H NMR δ: 3.47 (s, 3H), 5.08 (s, 2H), 5.91 (s, 2H), 6.49 (dd, 1H, *J* = 8.4 Hz, 2.4 Hz), 6.62 (d, 1H, *J* = 2.2 Hz), 6.70 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR δ: 55.9, 95.5, 99.7, 101.2, 108.0, 108.4, 142.5, 148.1, 152.5. HRMS calcd. for $C_9H_{10}O_4$: 182.0579; found: 182.05830.

4-Formyl-5-(methoxymethoxy)-1,3-benzodioxole (12)

BuLi (12.5 mL, 2.2 M) was added to a solution of 5.0 g (27.5 mmol) of **11** in dry THF (20 mL) at 0°C. The reaction mixture was stirred for 30 min and 1.5 equiv. of DMF (3.00 g, 3.18 mL) was added. The resulting mixture was stirred at room temperature for 4 h and quenched with 10 mL of NH_4Cl solution. Work-up gave the crude product as an orange powder. Purification by flash column chromatography (3:1, hexane:ethyl acetate) gave **12** as pale yellow crystals (4.9 g, 85%), mp 85–87°C. EI–MS (*m/z*, %): 210 ($M^{+\cdot}$, 92), 178 (53), 164 (82). IR (cm^{-1}): 1687. ^1H NMR δ: 3.48 (s, 3H), 5.17 (s, 2H), 6.09 (s, 2H), 6.58 (d, 1H, *J* = 8.6 Hz), 6.86 (d, 1H, *J* = 8.6 Hz), 10.35 (s, 1H). ^{13}C NMR δ: 56.4, 95.7, 102.9, 106.4, 111.7, 113.1, 143.4, 148.1, 153.6, 188.0. HRMS calcd. for $C_{10}H_{10}O_5$: 210.0528; found: 210.05317.

4-Hydroxy-5-(methoxymethoxy)-1,3-benzodioxole (13)

MCPBA (5.30 g, 30.7 mmol) was added in one portion to a solution of aldehyde **12** (3.00 g, 14. 3 mmol) in dry $CHCl_3$ (25 mL) at 0°C. The reaction mixture was warmed up to rt and stirred for 24 h, washed with sodium sulfite solution (sat., 2 × 15 mL), sodium bicarbonate (sat., 2 × 20 mL), and water (2 × 20 mL). The extract was dried over anhyd. $MgSO_4$, filtered, and evaporated to dryness. The resulting oily residue was purified by flash column chromatography (5:1, hexane:ethyl acetate) affording the expected formate ester as a pale yellow liquid (2.76 g, 91%). EI–MS (*m/z*, %): 226 ($M^{+\cdot}$, 6), 45 (100). IR (cm^{-1}): 1752. ^1H NMR δ: 3.45 (s, 3H), 5.06 (s, 2H), 5.96 (s, 2H), 6.64 (d, 1H, *J* = 8.6 Hz), 6.62 (d, 1H, *J* = 8.6 Hz), 8.24 (s, 1H). ^{13}C NMR δ: 56.2, 96.2, 102.3, 105.5, 108.5, 124.1, 139.8, 143.9, 144.6, 157.7. HRMS calcd. for $C_{11}H_{10}O_6$: 226.077; found: 226.04806.

To the above compound (20 mg, 0.94 mmol) in 5 mL of THF was added 25% NaOH solution (2 mL). The reaction mixture was stirred for 4 h at rt and extracted with water (4 × 5 mL). The resulting oily residue, obtained after usual work-up was purified using flash chromatography (9:1, hexane:ethyl acetate). Phenol **13** was obtained as a pale yellow liquid, (11 mg, 59%). EI–MS (*m/z*, %): 198 ($M^{+\cdot}$, 100), 166 (29), 153 (33). IR (cm^{-1}): 3540. ^1H NMR δ: 3.51 (s, 3H), 5.07 (s, 2H), 5.92 (s, 1H), 6.20 (s, 1H), 6.30 (d, 1H, *J* = 8.4 Hz), 6.54 (d, 1H, *J* = 8.4 Hz, the OH proton was not located). ^{13}C NMR δ: 56.5, 97.6, 99.2, 101.7, 109.4, 132.3, 134.5, 141.5, 144.5. HRMS calcd. for $C_9H_{10}O_5$: 198.0528; found: 198.05296.

5-Hydroxy-4-methoxy-1,3-benzodioxole (14)

Phenol **13** (4.9 g, 24.7 mmol) was *O*-methylated following the procedure for formation of **9**. The yield of 4-methoxy-5-methoxymethyl-1,3-benzodioxole, a pale yellow liquid, was 5.05 g, (96%). EI–MS (*m/z*, %): 212 ($M^{+\cdot}$, 100), 182 (89), 167 (69). ^1H NMR δ: 3.49 (s, 3H), 3.99 (s, 3H), 5.08 (s, 2H), 5.88 (s, 2H), 6.41 (d, 1H, *J* = 8.4 Hz), 6.57 (d, 1H, *J* = 8.6 Hz). ^{13}C NMR δ: 56.1, 60.1, 96.6, 101.2, 101.4, 110.1, 135.4, 137.7, 144.1, 144.2. HRMS calcd. for $C_{10}H_{12}O_5$: 212.0685; found: 212.0709.

The above compound (4.86 g, 22.9 mmol) in acetone (15 mL) containing 5.15 g, (34.3 mmol) of NaI was stirred for 30 min. 3 N Methanol HCl (40 mL) was added and the resulting reaction mixture stirred for 4 h. Most of the solvent was evaporated and the crude residue dissolved in water (10 mL). The aqueous phase was extracted with ether (3 × 15 mL) and the combined organic extracts were then washed with 10% NaOH solution (3 × 15 mL). The combined aqueous phase was acidified using conc. HCl and extracted with ether (3 × 20 mL). Further work-up afforded 2.81 g (73%) of **14** as pale orange crystals, mp 53–55°C. EI–MS (*m/z*, %): 168 (M^+, 100), 153 (76). IR (cm^{-1}): 3541. ^1H NMR δ: 4.02 (s, 3H), 5.43 (s, 1H), 5.87 (s, 2H), 6.39 (s, 2H). ^{13}C NMR δ: 59.9, 101.1, 101.8, 105.9, 131.4, 136.2, 142.1, 142.7. HRMS calcd. for $C_8H_8O_4$: 168.0422; found: 168.0408.

5-Hydroxy-4-methoxy-6-(2-propenyl)-1,3-benzodioxole (15)

A solution of **14** (2.55 g, 15.2 mmol), allyl bromide (2.0 mL, 23 mmol), and anhyd. K_2CO_3 (3.15 g, 23 mmol) in acetone (15 mL) was refluxed for 30 h. The solvent was removed under reduced pressure and the crude residue was dissolved in 20 mL water and 10 mL of 10% NaOH solution. Further work-up gave 5-*O*-allyl-4-methoxy-1,3-benzodioxole as a yellow liquid (2.72 g, 86%). EI–MS (*m/z*, %): 208 ($M^{+\cdot}$, 39), 167 (100). IR (cm^{-1}): 977, 929.; ^1H NMR δ: 3.97 (s, 3H), 4.47 (dt, 2H, *J* = 5.4 Hz, 1.4 Hz), 5.22 (ddt, 1H, *J* = 10.5 Hz, 1.6 Hz, 1.4 Hz), 5.35 (ddt, 1H, *J* = 17.3 Hz, 1.6 Hz, 1.6 Hz), 5.86 (s, 1H), 6.00–6.06 (m, 1H), 6.32 (d, 1H, *J* = 8.5 Hz), 6.38 (d, 1H, *J* = 8.5 Hz). ^{13}C NMR δ: 60.2, 71.2, 101.1, 101.2, 107.2, 117.5, 133.6, 134.9, 138.1, 143.4, 146.2. HRMS calcd. for $C_{11}H_{12}O_4$: 208.0736; found: 208.0755.

A solution of the above allyl ether (460 mg, 2.0 mmol) in 5 mL *N,N*-dimethylaniline was heated at 190°C for 2.5 h. The solution was cooled, diluted with 7 mL of ether, and washed several times with 10% NaOH solution. The alkaline extract was acidified with conc. HCl and extracted with ether (3 × 15 mL). The crude residue obtained after work-up was purified by flash column chromatography (9:1, hexane:ethyl acetate) to give **15** as pale yellowish liquid (400 mg, 87%). EI–MS (*m/z*,%): 208 ($M^{+\cdot}$, 100). IR (cm^{-1}): 926, 987. ^1H NMR δ: 3.30 (d, 2H, *J* = 6.6 Hz), 4.03 (s, 3H), 5.00–5.11 (m, 2H), 5.43 (s, 1H), 5.84 (s, 2H), 5.85–6.02 (m, 1H), 6.33 (s, 1H). ^{13}C NMR δ: 33.7, 59.9, 100.9, 102.8, 115.4, 117.5, 131.1, 143.2, 136.7, 139.9, 141.6. HRMS calcd. for $C_{11}H_{12}O_4$: 208.0736; found: 208.0731.

4,5-Dimethoxy-6-(2-propenyl)-1,3-benzodioxole (1)

The phenol **15** (140 mg, 0.70 mmol), K_2CO_3 (140 mg, 0.10 mmol), and 0.50 mL (0.8 mmol) of methyl iodide was reacted in 5 mL of acetone as with **9**. Work-up and chromatography gave 130 mg (80%) of **1**.

5-Allyloxy-4-formyl-1,3-benzodioxole (18)

To a solution of compound **17** (0.3 g, 1.68 mmol) in anhyd. THF (5 mL), *n*-BuLi (1.35 mL, 2.01 mmol, 1.5 molar solution in hexane) was added dropwise at 78°C. The resulting yellow solution was allowed to stir for 45 min and then *N,N*-dimethylformamide (0.26 mL, 3.37 mmol) was added. After 30 min, the reaction mixture was quenched with sat. NH_4Cl solution and extracted with ether. Flash column chromatography of the crude ether extracts using ethyl acetate:hexane (1:5) furnished the aldehyde **18** (302 mg, 87%) as a yellow solid, mp = 98–100°C. ^1H NMR: δ 4.52 (m, 2H), 5.25 – 5.34 (m, 2 H), 6.04 (s, 2H), 5.81–6.11 (m, 1H), 6.27 (d, 1H, *J* = 8.6 Hz), 6.83 (d, 1H, *J* = 8.5 Hz), 10.37 (s, 1H). ^{13}C NMR δ: 70.6, 103.5, 104.2, 111.7, 113.5, 118.5, 133.1, 143.2, 148.9 155.7, 188.8. HRMS calcd. for $C_{11}H_{10}O_4$: 206.0593; found: 206.0581.

5-Allyloxy-4-hydroxy-1,3-benzodioxole (19)

To a solution of aldehyde **18** (0.3 g, 1.45 mmol) in dry chloroform (5 mL) at 0°C, was added in one portion MCPBA (0.61 g, 1.74 mmol, 50%). The resulting mixture was stirred at 0°C for 24 h. The mixture was diluted with chloroform (20 mL) and was washed with sat. sodium sulfite (1 × 15 mL), sat. sodium bicarbonate solution (1 × 15 mL) and water (1 × 15 mL). The crude formate ester (0.25 g, 78%) was obtained as an oil and used for the next reaction without any further purification. ^1H NMR δ: 4.45 (m, 2H), 5.25 (m, 2 H), 5.96 (s, 2H), 5.95–6.01 (m, 1H), 6.34 (d, 1H, *J* = 8.5 Hz), 6.59 (d, 1H, *J* = 8.5 Hz), 8.24 (s, 1H). To a solution of the ester (0.25 g, 1.13 mmol) in THF (5 mL), was added 1 mL of a 3 N NaOH solution. The resulting homogeneous solution was stirred at rt for 1 h and was extracted with water (4 × 10 mL). The aqueous phase was then acidified with 2 N HCl and was extracted with CH_2Cl_2 (3 × 20 mL). Further work-up afforded an oily residue. Purification by silica gel flash column chromatography using ethyl acetate–hexane (1:5) as eluent gave **19** (0.15 g, 70%) as a yellow liquid. ^1H NMR δ: 4.48 (m, 2H), 5.32 (m, 2H), 5.92 (s, 2 H), 5.90–6.10 (m, 1 H), 6.30 (s, 2 H). ^{13}C NMR δ: 71.6, 99.3, 102.3, 105.3, 119.1, 132.2, 133.5, 137.1, 142.8, 144.0. HRMS calcd. for $C_{10}H_{10}O_4$:194.0593; found: 194.0602.

4,5-Dihydroxy-6-(2-propenyl)-1,3-benzodioxole (20)

A solution of **19** (0.15 g, 0.77 mmol) in *N,N*-dimethylaniline (2 mL) was heated at 190°C for 1 h and then was allowed to cool to rt The reaction mixture was extracted into ethyl acetate and was washed with 1 N HCl solution (3 × 10 mL), brine (2 × 10 mL), followed by water (10 mL). The crude rearranged product was purified via silica gel flash chromatography using ethyl acetate–hexane (3:7) as eluent to yield **20** (0.12 g, 79%) as a brown syrup. ^{1}H NMR δ: 3.31 (m, 2 H), 5.44 (m, 2H), 5.87 (s, 2H), 5.85–6.02 (m, 1H), 6.22 (s, 1H). ^{13}C NMR δ: 35.4, 101.82, 102.0, 116.7, 118.4, 129.6, 133.4, 137.1, 138.2, 142.6. HRMS calcd. for $C_{10}H_{10}O_4$: 194.0579; found 194.5965.

4,5-Dimethoxy-6-(2-propenyl)-1,3-benzodioxole (1)

To a solution of **20** (0.02 g, 0.103 mmol) in acetone (3 mL), was added sequentially potassium carbonate (28 mg, 0.21 mmol), and methyl iodide (0.10 mL, 0.206 mmol). The resulting reaction mixture was allowed to stirred at rt for 60 h. Solvent was removed under reduced pressure. The crude product obtained after the usual work-up was purified by silica gel flash column chromatography using ethyl acetate–hexane (1:5) as eluent to furnish the dillapiol (**1**) (18 mg, 82%) as a yellow liquid.

Reaction of 11 with disulfides

General procedure

*n*BuLi (1 equiv.) was added to 1 equiv. of **11** in THF at 0°C. After 30 min, 1.5 equiv. of disulfide was added and the solution was stirred for 1 h. Further work-up followed by silica gel chro-matography afforded the desired 4-thio derivatives.

4-Methylthio-5-methoxymethoxy-1,3-benzodioxole (21a)

This reaction was carried out starting with 5.0 g (27.5 mmol) of **11**. The yield of **21a**, a pale yellow liquid, was 5.70 g (91%). EI–MS (*m/z*, %): 228 (M^+, 100), 198 (63), 182 (17). ^{1}H NMR δ: 2.41 (s, 3H), 3.47 (s, 3H), 5.92 (s, 2H), 5.11 (s, 2H), 5.92 (s, 2H), 6.52 (d, 1H, *J* = 8.6 Hz), 6.59 (d, 1H, *J* = 8.6 Hz). ^{13}C NMR δ: 16.9, 56.1, 95.9, 101.2, 106.7, 107.8, 108.8, 142.3, 148.5, 151.7. HRMS calcd. for $C_{10}H_{12}O_4S$: 228.0456; found: 228.04679.

4-Phenylmethanethio-5-methoxymethoxy-1,3-benzodioxole (21b)

From 3.0 g, (16 mmol) of **11** and 5.35 g (22 mmol) of benzyl disulfide was obtained 2.37 g (58%) of **21b** as yellow oil. EI–MS (*m/z*, %): 304 (M^+, 29), 259 (18), 182 (26), 91 (100). ^{1}H NMR δ: 3.45 (s, 3H), 4.07 (s, 2H), 5.03 (s, 2H), 5.85 (s, 2H), 6.54 (d, 1H, *J* = 8.5 Hz), 6.63 (d, 1H, *J* = 8.5 Hz), 7.20 (s, 5H). ^{13}C NMR δ: 38.0, 56.1, 96.0, 101.2, 106.5, 107.4, 107.9, 126.9, 128.1, 128.8, 138.0, 142.2, 149.5, 152.5. HRMS calcd. for $C_{16}H_{16}O_4S$: 304.0792; found: 304.0758.

4-Phenylthio-5-methoxymethoxy-1,3-benzodioxole (21c)

Reaction of 1.50 g (8.0 mmol) of **11** (1.5 g, 8.0 mmol) and 1.80 g (8.0 mmol) of diphenyl disulfide gave 0.67 g (30%) of **21c** as white crystals, mp 67–69°C. EI–MS (*m/z*, %): 290 (M^+, 51), 260 (25), 91 (50). ^{1}H NMR δ: 3.33 (s, 3H), 5.05 (s, 2H), 5.93 (s, 2H), 6.63 (d, 1H, *J* = 8.5 Hz), 6.77 (d, 1H, *J* = 8.5 Hz), 7.08–7.20 (m, 5H). ^{13}C NMR δ: 56.1, 95.7, 101.6, 104.2, 1007.8 08.8, 125.5, 127.1, 128.7, 136.2, 142.5, 150.4, 152.7. HRMS calcd. for $C_{15}H_{14}O_4S$: 290.0613; found: 290.0600.

4-(4′-Methoxyphenylthio)-5-methoxymethoxy-1,3-benzodioxole (21d)

Reaction of 420 mg of **11** with 530 mg of *p*-methoxyphenyl disulfide gave 250 mg (40%) of **21d** as white crystals, mp 82–84°C. EI–MS (*m/z*, %): 320 (M^+, 8.6), 278 (46), 139 (100). ^{1}H NMR δ: 3.34 (s, 3H), 3.69 (s, 3H), 5.03 (s, 2H), 5.88 (s, 2H), 6.56 (d, 1H, *J* = 8.5 Hz), 6.68 (d, 1H, *J* = 8.5 Hz), 6.74 (d, 2H, *J* = 8.9 Hz), 7.22 (d, 2H, *J* = 8.9 Hz). ^{13}C NMR δ: 55.0, 55.9, 95.7, 101.4, 106.3, 107.7, 108.1, 114.2, 126.2, 130.7, 142.3, 149.8, 152.3, 158.3. HRMS calcd. for $C_{16}H_{16}O_5S$: 320.0718; found: 320.0706.

Removal of the MOM group

General procedure

Each MOM derivative **21** was dissolved in a mixture of acetone and 3 N methanolic HCl containing NaI. The mixture was stirred for about 4 h and most of the solvent was removed under reduced pressure. The residue was partitioned between ether and 10% NaOH solution. The basic extracts were acidified and reextracted with ether. The crude products obtained after further work-up were purified by recrystallization or chromatography.

5-Hydroxy-4-methylthio-1,3-benzodioxole

From 4.0 g of **21a** and 3.94 g of NaI in 15 mL of acetone and 40 mL of 3 N methanolic HCl was obtained 2.65 g (80%) of the title compound as a white powder, mp 51–53°C. EI–MS (*m/z*, %): 184 (M^+, 100), 169 (30). IR (cm^{-1}): 3428. ^{1}H NMR δ: 2.31 (s, 3H), 5.98 (s, 2H), 6.22 (s, 1H), 6.42 (d, 1H, *J* = 8.4 Hz), 6.69 (d, 1H, *J* = 8.4 Hz). ^{13}C NMR δ: 18.0, 101.6, 103.4, 105.4, 109.4, 140.7, 149.3, 151.2. HRMS calcd. for $C_8H_8O_3S$: 184.0194; found: 184.0163.

5-Hydroxy-4-phenylmethanethio-1,3-benzodioxole

Reaction of 2.51 g of **21b** with 1.86 g of NaI in 50 mL of acetone–methanol–conc. HCl (1:3:1) for 1 h afforded 1.68 g (91%) of the deprotected phenol as a yellowish oil. EI–MS (*m/z*, %): 260 (M^+, 36), 169 (8.2), 91 (100). IR (cm^{-1}): 3434. ^{1}H NMR δ: 3.87 (s, 2H), 5.85 (s, 2H), 6.03 (s, 1H), 6.35 (d, 1H, *J* = 8.4 Hz), 6.68 (d, 1H, *J* = 8.4 Hz), 7.10–7.25 (m, 5H). ^{13}C NMR δ: 39.3, 101.0, 101.5, 105.3, 109.8, 127.4, 128.4, 128.7, 137.2, 140.4, 149.8, 151.7. HRMS calcd. for $C_{14}H_{12}O_3S$: 260.0510; found: 260.0512.

5-Hydroxy-4-phenylthio-1,3-benzodioxole

Compound **21c** (670 mg, 2.3 mmol), 5.2 g of NaI in 10 mL of acetone and 8 mL of 3 N methanolic HCl was stirred for 1 h. The yield of the title compound, a white powder, mp 119–122°C, was >99%. EI–MS (*m/z*, %): 246 (M^+, 100), 162 (23), 140 (49). IR (cm^{-1}): 3441. ^{1}H NMR δ: 5.96 (s, 2H), 6.18 (s, 1H), 6.52 (d, 1H, *J* = 8.5 Hz), 6.81 (d, 1H, *J* = 8.6 Hz), 7.12–7.26 (m, 5H). ^{13}C NMR δ (ppm): 99.5, 101.9, 105.9, 110.8, 126.5, 127.0, 129.3, 134.2, 141.0,

150.1, 151.9. HRMS calcd. for $C_{13}H_{10}O_3S$: 246.0351; found: 246.0334.

5-Hydroxy-4-(4′-methoxyphenylthio)-1,3-benzodioxole

Compound **21d** (250 mg, 0.78 mmol) in acetone (10 mL) and 8 mL of 3 N methanolic HCl containing 180 mg NaI was stirred for 2 h. The yield of the above phenol (mp 82–83°C) was 180 mg (83%). EI–MS (*m/z*, %): 276 (M^+,100), 162 (18), 140 (44). IR (cm^{-1}): 3443. ^1H NMR δ: 3.74 (s, 3H), 5.94 (s, 2H), 6.31 (s, 1H), 6.47 (d, 1H, *J* = 8.5 Hz), 6.75 (d, 1H, *J* = 8.4 Hz), 6.79 (d, 1H, *J* = 6.9 Hz), 7.20 (d, 1H, *J* = 7.6 Hz). ^{13}C NMR δ: 55.3, 101.5, 101.7, 105.8, 110.4, 114.9, 124.5, 130.4, 140.9, 149.8, 151.6, 159.0. HRMS calcd. for $C_{14}H_{12}O_4S$: 276.0456; found: 276.0466.

Allylation of the 4-thio-5-hydroxy derivatives

General procedure

The above phenols were dissolved in acetone containing about 10–20% excess of anhydrous potassium carbonate. The mixture was refluxed for up to 24 h. The solvent was evaporated under reduced pressure and the residue was partitioned between ether and 10% NaOH solution. Further processing of the ether phase gave the desired product.

5-Allyoxy-4-methylthio-1,3-benzodioxole

From 1.89 g of 5-hydroxy derivative, series **a**, 2.13 g of potassium carbonate and 0.90 mL of allyl bromide in 15 mL acetone was obtained after 23 h of reflux, 2.03 g (88%) of the desired product as a clear liquid. EI–MS (*m/z*, %): 224.1 ($M^{+\cdot}$, 100), 184 (13), 137 (98). ^1H NMR δ: 2.46 (s, 1H), 4.53 (dt, 2H, *J* = 5.1 Hz, 1.4 Hz), 5.28 (dd, 1H, *J* = 10.5 Hz, 1.5 Hz), 5.44 (dd, 1H, *J* = 17.0 Hz, 1.6 Hz), 5.97 (s, 2H), 6.00–6.09 (m, 1H), 6.31 (d, 1H, *J* = 8.5 Hz), 6.63 (d, 1H, *J* = 8.5 Hz). ^{13}C NMR δ: 16.9, 70.3, 101.2, 104.5, 106.4, 117.4, 133.1, 133.8, 141.5, 148.7, 153.3. HRMS calcd. for $C_{11}H_{12}O_3S$: 224.0507; found: 224.0533.

5-Allyoxy-4-phenylmethanethio,3-benzodioxole

A solution of the 5-phenol, series **b** (1.68 g, 6.5 mmol), anhyd. K_2CO_3 (1.10 g, 8.0 mmol and 0.63 mL of allyl bromide in 15 mL of acetone when refluxed for 23 h, yielded 1.39 g (83%) of the desired allyl ether as a clear oil. EI–MS (*m/z*, %): 300 (M^+, 30), 259 (38), 91 (100). IR (cm^{-1}): 953, 995. ^1H NMR δ: 4.09 (s, 2H), 4.46 (d, 2H, *J* = 5.1 Hz), 5.27 (dd, 1H, *J* = 10.5 Hz, 1.5 Hz), 5.43 (dd, 1H, *J* = 15.6 Hz, 1.6 Hz), 5.84 (s, 2H), 5.95–6.11 (m, 1H), 6.30 (d, 1H, *J* = 8.4 Hz), 6.62 (d, 1H, *J* = 9.2 Hz), 7.21 (s, 5H). ^{13}C NMR δ: 37.9, 70.3, 101.1, 104.6, 105.5, 107.1, 117.3, 126.8, 128.1, 128.8, 133.1, 138.0, 141.3, 149.7, 153.9. HRMS calcd. for $C_{17}H_{16}O_3S$: 300.0821; found: 300.0820.

5-Allyoxy-4-phenylthio-1,3-benzodioxole

A mixture of phenol, series **c** (1.62 g, 6.6 mmol), anhyd. K_2CO3 (1.10 g, 8.0 mmol), and 0.63 mL of allyl bromide when refluxed for 23 h in acetone (15 mL) gave 1.25 g (84%) of the expected allyl ether. EI–MS (*m/z*, %): 268 ($M^{+\cdot}$, 52), 245 (52), 91 (100). IR (cm^{-1}): 943, 996. ^1H NMR δ: 4.44 (dt, 2H, *J* = 5.0 Hz, 1.6 Hz), 5.15 (ddt, 1H, *J* = 10.5 Hz, 1.6 Hz, 1.5 Hz), 5.25 (ddt, 1H, *J* = 17.0 Hz, 1.7 Hz, 1.6 Hz), 5.76–5.95 (m, 1H), 5.93 (s, 2H), 6.35 (d, 1H, *J* = 8.5 Hz), 6.75 (d, 1H, *J* = 8.5 Hz), 7.07–7.22 (m, 5H). ^{13}C NMR δ: 70.3, 101.6, 103.5, 104.9, 108.4, 117.2, 125.4, 127.3, 128.6, 132.8, 136.2, 141.7, 150.5, 145. HRMS calcd. for $C_{16}H_{14}O_3S$: 286.0664; found: 286.0649.

5-Allyoxy-4-(4′-methoxyphenylthio)-1,3-benzodioxole

Reaction of the phenol, series **d** (1.10 g, 4.0 mmol), anhyd. K_2CO_3 (0.83 g, 6.0 mmol) and 0.41 mL of allyl bromide in acetone (15 mL) at reflux for 23 h gave 0.96 g (76%) of the expected product as a clear oil. EI–MS (*m/z*, %): 316 ($M^{+\cdot}$, 32), 275 (30), 149 (100). IR (cm^{-1}): 931, 953. ^1H NMR δ: 3.72 (s, 3H), 4.43 (dt, 2H, *J* = 5.1 Hz, 1.5 Hz), 5.18 (ddt, 1H, *J* = 12 Hz, 1.6 Hz, 1.5 Hz), 5.31 (ddt, 1H, *J* = 18 Hz, 1.7 Hz, 1.6 Hz), 5.90 (s, 2H), 5.83–5.97 (m, 1H), 6.30 (d, 1H, *J* = 8.5 Hz), 6.67 (d, 1H, *J* = 8.5 Hz), 6.75 (d, 2H, *J* = 9.0 Hz), 7.26 (d, 2H, *J* = 9.0 Hz). ^{13}C NMR δ: 55.1, 70.3, 101.4, 104.8, 105.6, 107.8, 114.2, 117.2, 126.3, 131.0, 132.9, 141.6, 149.9, 153.7, 158.4. HRMS calcd. for $C_{17}H_{16}O_4S$: 316.0770; found: 316.0766.

Claisen rearrangement of the 5-allyl ethers

General procedure

The 5-allyl ethers obtained as described above were dissolved in a small quantity of *N,N*-dimethylaniline and heated to 190°C for 1–3 h. The cooled reaction mixture was diluted with ether and extracted with 10% NaOH solution. The combined basic extracts were acidified and extracted with ether. Further work-up and purification yielded the desired Claisen rearrangement products.

5-Hydroxy-4-methylthio-6-(2-propenyl)-1,3-benzodioxole (22a)

Allyl ether, series **a** (1.0 g, 4.0 mmol) when heated in 5 mL of *N,N*-dimethylaniline (5 mL) at 190°C for 2.5 h, gave 0.87 g (87%)of **22a** as a colourless liquid. EI–MS (*m/z*, %): 224 ($M^{+\cdot}$, 100), 197 (9), 176 (18). IR (cm^{-1}): 927, 953, 3425. ^1H NMR δ (ppm): 2.31 (s, 3H), 3.32 (dt, 2H, *J* = 6.8 Hz, 1.4 Hz), 5.01–5.11 (m, 2H), 5.95 (s, 2H), 5.88–6.02 (m, 1H), 6.40 (s, 1H), 6.62 (s, 1H).^{13}C NMR δ: 18.0, 34.4, 101.3, 102.9, 110.4, 115.5, 117.1, 136.6, 140.3, 147.5, 148.2. HRMS calcd. for $C_{11}H_{12}O_3S$: 224.0507; found: 224.0493.

5-Hydroxy-4-phenylmethanethio-6-(2-propenyl)-1,3-benzodioxole (22b)

Allyl ether, series **b** (4.30 g, 14.0 mmol) when treated as above gave 0.42 g (98%) of **22b** as a colourless oil. EI–MS (*m/z*, %): 300 (M^+, 48), 224 (91), 209 (28), 176 (48). IR (cm^{-1}): 954, 997, 1638, 3429. ^1H NMR δ: 3.25 (d, 2H, *J* = 6.4 Hz), 3.87 (s, 2H), 4.93–5.04 (m, 2H), 5.82–5.96 (m, 1H), 5.83 (s, 2H), 6.18 (s, 1H), 6.61 (s, 1H), 7.08–7.25 (m, 5H). ^{13}C NMR δ: 34.4, 39.4, 100.6, 101.2, 10.9, 115.3, 116.9, 127.4, 128.5, 128.7, 136.6, 137.2, 140.1, 148.0, 148.8. HRMS calcd. for $C_{17}H_{16}O_3S$: 300.0821; found: 300.08240.

5-Hydroxy-4-phenylthio-6-(2-propenyl)-1,3-benzodioxole (22c)

From 1.5 g of allyl ether, series **c**, was obtained 550 mg (37%) of **22c** as a pale yellow oil. EI–MS (*m/z*, %): 286 (M^+, 100), 162 (8). IR (cm^{-1}): 953, 997, 1638, 3443. ^1H NMR δ: 3.35 (dt, 2H, *J* = 6.4 Hz, 1.4 Hz), 5.05–5.09

(m, 2H), 5.92 (s, 2H), 5.93–5.99 (m, 1H), 6.31 (s, 1H), 6.73 (s, 1H), 7.13–7.23 (m, 5H). ^{13}C NMR δ: 34.4, 99.0, 101.5, 111.9, 115.7, 117.6, 126.5, 127.0, 129.3, 134.3, 136.5, 40.6, 148.3, 148.9. HRMS calcd. for $C_{16}H_{14}O_3S$: 286.0664; found: 286.0641.

5-Hydroxy-4-(4′-methoxyphenylthio)-6-(2-propenyl)-1,3-benzodioxole (22d)

The allyl ether from series **d** (310 mg, 0.9 mmol) when heated for 2.5 h in 3 mL of *N*,*N*-dimethylaniline gave 0.29 g (97%) of **22d** as pale yellow oil. EI–MS (*m/z*, %): 316 (M^+, 100), 208 (22), 180 (47). IR (cm^{-1}): 949, 995, 1638, 3440. ^{1}H NMR δ: 3.32 (d, 2H, *J* = 6.5 Hz), 3.74 (s, 3H), 5.02 (s, 1H), 5.05 (d, 2H, *J* = 6 Hz), 5.91 (s, 2H), 5.89–5.97 (m, 1H), 6.42 (s, 3H), 6.67 (s, 1H), 6.78 (d, 2H, *J* = 8.7 Hz), 7.19 (d, 2H, *J* = 8.7 Hz). ^{13}C NMR δ: 34.5, 55.4, 101.1, 101.5, 111.5, 114.9, 115.6, 117.5, 124.7, 130.4, 136.6, 140.6, 148.0, 148.7, 159.0. HRMS calcd. for $C_{17}H_{16}O4S$: 316.0770; found: 316.0749.

Methylation of phenols (22)

These reactions were carried out in the same manner as the conversion **8** to **9**.

5-Methoxy-4-methylthio-6-(2-propenyl)-1,3-benzodioxole (23a)

Phenol **22a** (400 mg, 1.8 mmol), was converted in 87% yield (372 mg) to **23a**. EI–MS (*m/z*, %): 238 (M^+,100), 223 (13), 176 (41). IR (cm^{-1}): 949, 996. ^{1}H NMR δ: 2.45 (s, 3H), 3.30 (dt, 2H, *J* = 6.5 Hz, 1.4 Hz), 3.75 (s, 3H), 5.01–5.05 (m, 2H), 5.93 (s, 2H), 5.84–5.92 (m, 1H), 6.53 (s, 1H). ^{13}C NMR δ: 16.9, 34.0, 61.4, 101.3, 108.2, 112.3, 115.7, 125.8, 137.1, 143.4, 146.8, 151.8. HRMS calcd. for $C_{12}H_{14}O_3S$: 238.0664; found: 238.0682.

5-Methoxy-4-phenylmethanethio-6-(2-propenyl)-1,3-benzodioxole (23b)

Phenol **22b** (420 mg, 1.4 mmol) was converted into 0.420 mg (96%) of **23b**. EI–MS (*m/z*, %): 314 ($M^{+\cdot}$, 72), 223 (11), 91 (100). IR (cm^{-1}): 950, 994, 1638. ^{1}H NMR δ: 3.30 (dt, 2H, *J* = 6.4 Hz, 1.5 Hz), 3.65 (s, 3H), 4.12 (s, 2H), 4.96–5.07 (m, 2H), 5.88 (s, 2H), 5.83–5.95 (m, 1H), 6.55 (s, 1H), 7.17–7.24 (m, 5H). ^{13}C NMR δ: 34.0, 37.9, 61.6, 101.3, 108.9, 109.9, 115.7, 125.7, 127.0, 128.3, 128.9, 137.2, 138.0, 43.2, 147.6, 152.5. HRMS calcd. for $C_{18}H_{18}O_3S$: 314.0977; found: 314.0953.

5-Methoxy-4-phenylthio-6-(2-propenyl)-1,3-benzodioxole (23c)

The title compound **23c** was obtained as a yellowish oil in 87% yield starting with 550 mg of **22c**. EI–MS (*m/z*, %): 300 ($M^{+\cdot}$, 100), 176 (48), 162 (15). IR (cm^{-1}): 948, 995, 1639. ^{1}H NMR δ: 3.35 (dt, 2H, *J* = 6.4 Hz, 1.4 Hz), 3.73 (s, 3H), 5.02–5.11 (m, 2H), 5.91 (s, 2H), 5.86–6.05 (m, 1H), 6.71 (s, 1H), 7.10–7.22 (m, 5H). ^{13}C NMR δ: 34.2, 62.2, 101.6, 107.6, 110.4, 116.0, 125.6, 126.2, 127.1, 128.9, 136.2, 137.1, 143.7, 148.6, 153.2. HRMS calcd. for $C_{17}H_{16}O_3S$: 300.0821; found: 300.0802.

5-Methoxy-4-(4′-methoxyphenylthio)-6-(2-propenyl)-1,3-benzodioxole (23d)

Phenol **22d** (170 mg) was converted in 96% yield into **23d** as a pale yellow oil. EI–MS (*m/z*, %): 330 ($M^{+\cdot}$, 100), 176 (21), 121 (68). IR (cm^{-1}): 949, 995, 1638. ^{1}H NMR δ: 3.34 (dt, 2H, *J* = 6.5 Hz, 1.5 Hz), 3.73 (s, 3H), 3.75 (s, 3H), 5.03–5.07 (m, 2H), 5.87 (s, 2H), 5.88–5.94 (m, 1H), 6.63 (s, 1H), 6.77 (d, 2H, *J* = 8.9 Hz), 7.24 (d, 2H, *J* = 8.9 Hz). ^{13}C NMR δ: 34.1, 55.2, 62.0, 101.5, 109.7, 109.8, 114.5, 115.9, 126.0, 126.3, 130.7, 137.1, 143.6, 148.1, 152.7, 158.5. HRMS calcd. for $C_{18}H_{18}O_4S$: 330.0926; found: 330.0942.

Oxidation of the sulfides (23) to sulfoxides (24) and sulfones (25)

General procedures

For the oxidation to the sulfoxides, a solution of the sulfide in ethyl acetate was cooled to approx. –40°C and 1.2 equiv. of MCPBA was added. The reaction mixture was allowed to warm to rt and stirred for 24 h. Work-up consisted of washing first with sat. sodium bisulfite solution, then with sat. sodium bicarbonate, and finally with water. The organic soluble product was purified by column chromatography.

The oxidation to sulfones was carried out with 3–4 equiv. of MCPBA in ethyl acetate at rt for 24 h. The work-up of the reaction mixture was similar to that of the sulfoxides.

5-Methoxy-4-methylsulfinyl-6-(2-propenyl)-1,3-benzodioxole (24a)

Sulfide **23a** (100 mg, 0.42 mmol) was reacted with 0.5 mmol of MCPBA in 6 mL of ethyl acetate to afford 67 mg (63%) of **24a** as a pale yellowish liquid. EI–MS (*m/z*, %): 254 ($M^{+\cdot}$, 83), 237 (100). IR (cm^{-1}): 942, 994, 1050. ^{1}H NMR δ: 3.01 (s, 3H), 3.16 (dd, 2H, *J* = 6.4 Hz, 1.5 Hz), 3.78 (s, 3H), 5.03–5.09 (m, 2H), 5.84–5.89 (m, 1H), 6.06 (s, 2H), 6.74 (s, 1H). ^{13}C NMR δ: 33.1, 39.7, 63.4, 102.7, 112.3, 116.5, 120.8, 126.1, 136.3, 145.0, 145.5, 149.1. HRMS calcd. for $C_{12}H_{14}O_4S$: 254.0613; found: 254.0607.

5-Methoxy-4-methylsulfonyl-6-(2-propenyl)-1,3-benzodioxole (25a)

Oxidation of 50 mg, (0.21 mmol) of sulfide **23a** afforded 45 mg (80%) of sulfone **25a** as a pale yellow solid. EI–MS (*m/z*, %): 270 ($M^{+\cdot}$, 100). IR (cm^{-1}): 950, 993, 1136, 1316. ^{1}H NMR δ: 3.26 (s, 3H), 3.54 (d, 2H, *J* = 6.5 Hz), 3.84 (s, 3H), 5.06–5.13 (m, 2H), 5.84–5.92 (m, 1H), 6.05 (s, 2H), 6.83 (s, 1H). ^{13}C NMR δ: 32.1, 44.8, 63.8, 102.8, 113.9, 117.0, 118.1, 127.0, 135.9, 145.0, 145.2, 149.2. HRMS calcd. for $C_{12}H_{14}O_5S$: 270.0562; found: 270.0541.

5-Methoxy-4-phenylmethanesulfinyl-6-(2-propenyl)-1,3-benzodioxole (24b)

From 110 mg, (0.4 mmol) of **23b** was obtained 70 mg (61%) of sulfoxide **24b** as a yellowish oil. EI–MS (*m/z*, %): 330 ($M^{+\cdot}$, 21), 283 (47), 91 (100). IR (cm^{-1}): 951, 992, 1049, 1071. ^{1}H NMR (500 MHz) δ: 3.24 (d, 2H, *J* = 6.3 Hz), 3.56 (s, 3H), 4.34 (d, 1H, *J* = 12.5 Hz), 4.45 (d, 1H, *J* = 12.5 Hz), 5.00–5.06 (m, 2H), 5.82 (d, 1H, *J* = 1.34), 5.90 (d, 1H, *J* = 1.4 Hz), 5.81–5.87 (m, 1H), 6.67 (s, 1H), 7.10–7.24 (m, 5H). ^{13}C NMR δ: 33.0, 59.2, 63.0, 102.6, 112.3, 116.3, 118.6,

125.8, 128.1, 128.4, 130.2, 130.3, 136.4, 145.2, 145.8, 149.4. HRMS calcd. for $C_{18}H_{18}O_4S$: 330.0926; found: 330.0910.

5-Methoxy-4-phenylmethanesulfonyl-6-(2-propenyl)-1,3-benzodioxole (25b)

Oxidation of 80 mg (0.25 mmol) of sulfide **23b** in 6 mL of ethyl acetate gave 40 mg (45%) of sulfone **25b** as a white solid, mp 133–136°C. EI–MS (*m/z*, %): 346 ($M^{+\cdot}$, 34), 139 (16), 91 (100). IR (cm^{-1}): 1149, 1320. ^1H NMR δ: 3.35 (d, 2H, *J* = 6.4 Hz), 3.88 (s, 3H), 4.57 (s, 2H), 5.05–5.15 (m, 2H), 5.82 (s, 2H), 5.88–5.93 (m, 1H), 6.77 (s, 1H), 7.20–7.24 (m, 5H). ^{13}C NMR δ: 33.2, 62.2, 63.9, 102.6, 114.1, 116.8, 126.7, 128.1, 128.3, 128.5, 130.9, 133.9, 144.9, 146.3, 1494. HRMS calcd. for $C_{18}H_{18}O_5S$: 346.0875; found: 346.0852.

5-Methoxy-4-lphenylsulfinyl-6-(2-propenyl)-1,3-benzodioxole (24c)

Sulfide **23c** (100 mg, 0.30 mmol) was oxidized to sulfoxide **24c**, mp 83–87°C, in 76% yield. EI–MS (*m/z*, %): 316 ($M^{+\cdot}$, 39), 299 (100), 190 (59). IR (cm^{-1}): 948, 994, 1054,1639. ^1H NMR δ: 3.29 (d, 2H, *J* = 6.4 Hz), 3.85 (s, 3H), 5.00–5.07 (m, 2H), 5.82 (s, 1H), 5.82–5.88 (m, 1H), 5.97 (s, 1H), 6.68 (s, 1H), 7.24–7.71 (m, 5H). ^{13}C NMR δ: 33.0, 63.2, 102.6, 112.4, 116.5, 124.3, 125.8, 128.8, 130.3, 136.2, 143.8, 145.4. HRMS calcd. for $C_{17}H_{16}O_4S$: 316.0770; found: 316.0766.

5-Methoxy-4-phenylsulfonyl-6-(2-propenyl)-1,3-benzodioxole (25c)

Oxidation of 90 mg (0.21 mmol) of sulfide **23c** in ethyl acetate (6 mL) with 2 equiv. of MCPBA for 24 h provided the sulfone **25c** as a white solid, mp 86–88°C, in 71% yield. EI–MS (*m/z*, %): 332 ($M^{+\cdot}$, 100), 176 (34). IR (cm^{-1}): 992, 953, 1148, 1319. ^1H NMR δ: 3.23 (dt, 2H, *J* = 6.4 Hz, 1.5 Hz), 3.80 (s, 3H), 5.03–5.07 (m, 2H), 5.77–5.82 (m, 1H), 6.08 (s, 2H), 6.78 (s, 1H), 7.41–7.57 (m, 5H). ^{13}C NMR δ: 33.0, 63.6, 102.8, 114.0, 116.9, 118.7, 126.9, 127.5, 128.7, 133.2, 136.0, 142.6, 145.0, 145.4, 149.3. HRMS calcd. for $C_{17}H_{16}O_5S$: 332.0719; found: 332.0699.

5-Methoxy-4-(4′-methoxyphenylsulfinyl)-6-(2-propenyl)-1,3-benzodioxole (24d)

Sulfide **23d** (140 mg) was oxidized to give 100 mg (68%) of sulfoxide **25c** as a pale yellow oil. EI–MS (*m/z*, %): 330 ($M^{+\cdot}$, 60), 190 (28), 121 (100). IR (cm^{-1}): 949, 993,1044,1639. ^1H NMR δ: 3.27 (dt, 2H, *J* = 6.4 Hz, 1.4 Hz), 3.77 (s, 3H), 3.82 (s, 3H), 4.99–5.06 (m, 2H), 5.81–5.84 (m, 1H), 5.87 (s, 1H), 5.98 (s, 1H), 6.66 (s, 1H), 6.92 (d, 2H, *J* = 8.9 Hz), 7.64 (d, 2H, *J* = 8.9 Hz). ^{13}C NMR δ: 33.1, 55.4, 63.2, 102.6, 112.1, 114.4, 116.5, 122.1, 125.9, 126.4, 135.4, 136.4, 144.7, 145.5, 149.2, 161.5. HRMS calcd. for $C_{18}H_{18}O_5S$: 346.0875; found: 346.0875.

5-Methoxy-4-(4′-methoxyphenylsulfonyl)-6-(2-propenyl)-1,3-benzodioxole (25d)

Sulfide **23d** (90 mg) was oxidized to sulfone **25d**, mp 82–85°C, in 71% yield. EI–MS (*m/z*, %): 362 ($M^{+\cdot}$, 38), 300 (100), 176 (52). IR (cm^{-1}): 953, 992, 1145, 1315. ^1H NMR δ: 3.22 (dt, 2H, *J* = 6.4 Hz, 1.4 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 4.99–5.07 (m, 2H), 5.75–5.83 (m, 1H), 6.05 (s, 2H), 6.92 (s, 1H), 6.84 (d, 2H, *J* = 8.9 Hz), 7.93 (d, 2H, *J* = 8.9 Hz). ^{13}C NMR δ: 33.1, 55.5, 63.6, 102.7, 113.7, 113.9, 116.9, 126.9, 129.8, 134.4, 136.0, 144.9, 145.1, 149.2, 163.4. HRMS calcd. for $C_{18}H_{18}O_6S$: 362.0824; found: 362.0821.

5-Hydroxy-4-hydroxymethyl-6-(2-propenyl)-1,3-benzodioxole (26)

To a solution of the aldehyde **8** (238 mg, 1.15 mmol) in 2.5 mL of ethanol was added 44 mg of sodium borohydride. The solution was stirred for 40 min, diluted with 2 mL of water, and then acidified with 2 N HCl. Work-up afforded 256 mg of crude product which was purified by chromatography to yield 198 mg (83%) of **26** as a white solid, mp 82–84°C. EI–MS (*m/z*, %): 208 ($M^{+\cdot}$, 26), 190 (100), 189 (50). IR (cm^{-1}): 3404, 3587. ^1H NMR δ: 2.55 (s, 1H), 3.28 (dt, *J* = 6.5, 1.4 Hz), 4.81 (s, 2H), 5.05–5.10 (m, 2H), 5.83 (s, 2H), 5.91–5.96 (m, 1H), 6.53 (s, 1H), 6.85 (s, 1H). ^{13}C NMR δ: 34.2, 57.8, 101.0, 108.9, 115.7, 118.3, 136.9, 140.4, 143.3, 148.8. HRMS calcd. for $C_{11}H_{12}O_4$: 208.0736; found: 208.0736.

5-Hydroxy-4-(1-hydroxyoctyl)-6-(2-propenyl)-1,3-benzodioxole (27)

A solution of 300 mg (1.45 mmol) of aldehyde **8** in 2 mL of ether was added to a freshly prepared solution (approx. 3 mmol) of *n*-octylmagnesium bromide in 3 mL of ether. The reaction mixture was refluxed for 45 min and quenched with sat. NH_4Cl solution. Work-up afforded 108 mg (25%) of **27**, mp 91–93°C. EI–MS: (*m/z*, %): 320 ($M^{+\cdot}$-H_2O, 100), 191 (53). IR (cm^{-1}): 3372, 3586. ^1H NMR δ: 0.86 (t, 3H, *J* = 6.7 Hz), 1.24–1.33 (m, 11H), 1.41–1.46 (m, 1H), 1.75–1.81 (m, 1H), 1.85–1.91 (m, 1H), 2.54 (s, 1H), 3.23–3.33 (m, 2H), 5.02–5.07 (m, 3H), 5.79 (d, 1H, *J*= 1.3 Hz), 5.83 (d, 1H, *J* = 1.4 Hz), 5.91–5.99 (m, 1H), 6.52 (s, 1H), 7.65 (d, 1H, *J* = 4.5 Hz). ^{13}C NMR δ: 14.1, 22.6, 25.5, 29.2, 29.3, 29.5, 31.8, 33.9, 36.6, 70.4, 100.8, 108.4, 111.4, 115.4, 119.0, 137.1, 139.8, 142.6, 147.8. HRMS calcd. for $C_{19}H_{28}O_4$: 320.1998; found: 320.1998.

4-Hydroxymethyl-5-methoxy-6-(2-propenyl)-1,3-benzodioxole (28)

The aldehyde **9** (350 mg) was reduced with $NaBH_4$ following the procedure for **8** to give **28** as an oil in 75% purified yield. IR (cm^{-1}): 3598. ^1H NMR δ: 2.45 (s, 1H), 3.30 (dt, 2H, *J* = 6.5, 1.4 Hz), 3.72 (s, 3H), 4.68 (s, 2H). ^{13}C NMR δ: 33.6, 55.7, 62.5, 101.4, 108.9, 115.9, 116.4, 125.4, 137.2, 143.7, 144.7, 150. EI–MS (*m/z*, %): 222 ($M^{+\cdot}$, 100). HRMS calcd. for $C_{12}H_{14}O_4$: 222.0892; found: 222.0906.

4-(1-Hydroxyoctyl)-5-methoxy-6-(2-propenyl)-1,3-benzodioxole (29)

This compound was prepared in 68% yield in a manner similar to the preparation of **27**. The yield of **29**, a clear yellowish oil, was 65%. EI–MS (*m/z*, %): 334 ($M^{+\cdot}$, 5), 316 (100), 190 (42), 43 (75). IR (cm^{-1}): 3588. ^1H NMR δ: 0.84–0.87 (m, 3H), 1.24–1.30 (m, 11H), 1.45–1.50 (m, 1H), 1.76–1.78 (m, 1H), 1.90–1.91 (m, 1H), 3.31 (dd, 2H, *J* = 6.4, 1.0 Hz), 3.70 (s, 3H), 4.88 (s, 1H), 5.02–5.06 (m, 2H), 5.87–5.93 (m, 1H), 5.91 (s, 2H), 6.56 (s, 1H). ^{13}C NMR δ: 14.1,

22.6, 26.1, 29.2, 29.5, 29.7, 31.9, 33.7, 37.6, 62.5, 68.3, 101.3, 108.4, 115.9, 120.8, 125.5, 137.2, 143.6, 143.9, 149.7. HRMS calcd. for $C_{20}H_{30}O_4$: 334.2145; found: 334.2157.

Cinnamate ester (30)

Methyl (triphenylphosphoranylidene)acetate (0.16 g, 0.47 mmol) was added to a solution of aldehyde **24** (85.5 mg, 0.39 mmol) in toluene (2 mL) and the mixture was refluxed for 22 h. After this time, the mixture was cooled to rt and the solvent was removed under vacuum. Purification by flash chromatography (5:1, hexane–ethyl acetate) afforded the desired product **30** as a pale yellow solid, mp 76–78°C, (98.4 mg, 91%). EI–MS (*m/z*, %): 276 ($M^{+\cdot}$, 100), 245 (41). IR (cm^{-1}): 1713 ^1H NMR δ: 3.32 (dt, 2H, J = 6,5, 1.4 Hz), 3.69 (s, 3H), 3.79 (s, 3H), 5.03–5.07 (m, 2H), 5.87–5.93 (m, 1H), 6.00 (s, 2H), 6.66 (s, 1H), 6.78 (d, 1H, J = 16.3 Hz), 7.81 (d, 1H, J = 16.3 Hz). ^{13}C NMR δ: 33.6, 51.6, 62.7, 101.8, 110.7, 112.3, 116.0, 121.8, 125.5, 135.0, 137.0, 143.9, 145.6, 151.2, 167.9. HRMS calcd. for $C_{15}H_{16}O_5$: 276.0998; found: 276.0999.

5-Methoxy-4-octyloxy-6-(2-propenyl)-1,3-benzodioxide (31)

A solution of phenol **10** (88 mg), K_2CO_3 (90 mg), and octyl bromide (0.09 mL) in 6 mL of acetone was refluxed for 64 h. The acetone was evaporated and the residue partitioned between water and ether. The yield of **31**, a yellow oil, was 60%. EI–MS (*m/z*, %): 320 ($M^{+\cdot}$, 64), 208 (74), 84 (62), 49 (100). ^1H NMR δ: 0.87 (t, 3H, J = 6.8 Hz), 1.24–1.32 (m, 8H), 1.42–1.45 (m,2H), 1.72–1.75 (m, 2H), 3.29 (dt, 2H), J = 6.6, 1.1 Hz), 3.75 (s, 3H), 4.16 (t, 2H, J = 6.7 Hz), 5.00–5.04 (m, 2H), 5.85 (s, 2H), 5.87–5.93 (m, 1H), 6.33 (s, 1H). ^{13}C NMR δ: 14.1, 22.6, 25.8, 29.2, 29.3, 30.1, 31.8, 34.0, 61.2, 72.6, 101.0, 102.7, 115.4, 126.0, 136.3, 136.9, 137.5, 144.4, 144.7. HRMS calcd. for $C_{19}H_{28}O_4$: 320.1988; found: 320.1984.

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