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Synthesis of Diverse 6-Oxa-allocolchicinoids by a Suzuki–Miyaura Coupling, Acid-Catalyzed Intramolecular Transacetalization Strategy

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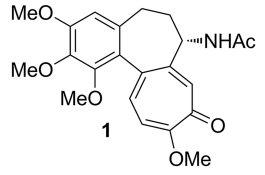
The synthesis of allocolchicine analogues is of importance as these compounds have been found to possess promising anticancer activity by affecting tubulin polymerization. In this paper, the synthesis of 28 novel substituted 6-oxa-allocolchicinoids is reported. The key steps involved in the synthesis were a Suzuki–Miyaura coupling reaction, followed by an acid-catalyzed intramolecular transacetalization to afford the desired 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines. In addition, when thiophenol and phenol were used in the transacetalization step, the 5-(phenylsulfanyl)-5,7-dihydrodibenzo[*c*,*e*]oxepine and 4-(5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenol skeletons were obtained, respectively. The cytotoxicity of the synthetic compounds was unfortunately not impressive; however, one of the compounds was shown to sensitize vincristine-resistant leukemia and lymphoma cells to vincristine, a result vindicating further synthetic studies.

1. Introduction

Colchicine (**1**) and the related compound allocolchicine (**2a**) have generated considerable interest due to their cytotoxicity, particularly in the cancer research arena (Figure 1).[1] Both compounds were found to be tubulin-assembly inhibitors, in this way disrupting cell cycles and inducing apoptosis.[2] For this reason, numerous research groups have attempted total syntheses of these natural products, as well as the generation of analogues with novel, but controllable, bioactivities. Although colchicine (**1**) has seen the bulk of interest, in recent years allocolchicine (**2a**) has been the inspiration for the synthesis of a variety of analogues.[3]

Due to these interesting bioactivities, allocolchicine (**2a**), *N*-acetylcolchicinol (*N*-acetylcolchinol, **2b**), its methylated derivative **2c** and more soluble clinically applied analogues such as **2d**, have been synthesized.[4] In addition, novel synthetic targets have included allocolchicinoids with modified



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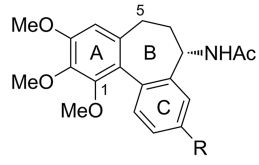

2a: R = CO_2Me (Allocolchicine)
2b: R = OH (*N*-acetylcolchicinol)
2c: R = OMe (*N*-acetylcolchicinol methyl ether)
2d: R = OPO_3H_2 (ZD6126)

Figure 1. Structures of colchicine (**1**) and allocolchicines **2**.

B-,[5] B,C-[6] and C-ring[7] systems, and even "B-ring-opened"[8] analogues have been synthesized and tested.

In terms of relevant examples, in 2009, Schmalz and coworkers described synthetic access to a series of 6-oxa-allocolchicinoids, which were synthesized by an innovative [2+2+2] cycloaddition (Figure 2a).[9] These compounds were found to have interesting apoptosis-inducing properties. Furthermore, papers by Baudoin[10] and Wallace[11] (Figure 2b) demonstrated how suitably substituted dibenzo[*c*,*e*]oxepine skeletons gave rise to 6-oxa-allocolchicinoids with potent biological activities. For both papers, an acid-mediated ring-closure afforded the seven-membered B-ring system (as indicated for Wallace's compound shown in Figure 2b). Note should also be taken of work by Heo and

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co-workers, who utilized a sequential Suzuki–Miyaura coupling/aldol condensation strategy to synthesize a series of dibenzo[*a*,*c*]cyclohepten-5-ones, although these compounds appear not to have been tested for their ability to affect tubulin polymerization (Figure 2c).[12a] The work by Heo et al. entailed an in-depth study on the key coupling conditions, based on the biaryl coupling/cyclization strategies towards the dibenzo[*c*,*e*]oxepine skeleton, so elegantly utilized by Leonard[13] and Kocienski[14] in their asymmetric syntheses of *N*-acetylcolchicinol (**2b**).

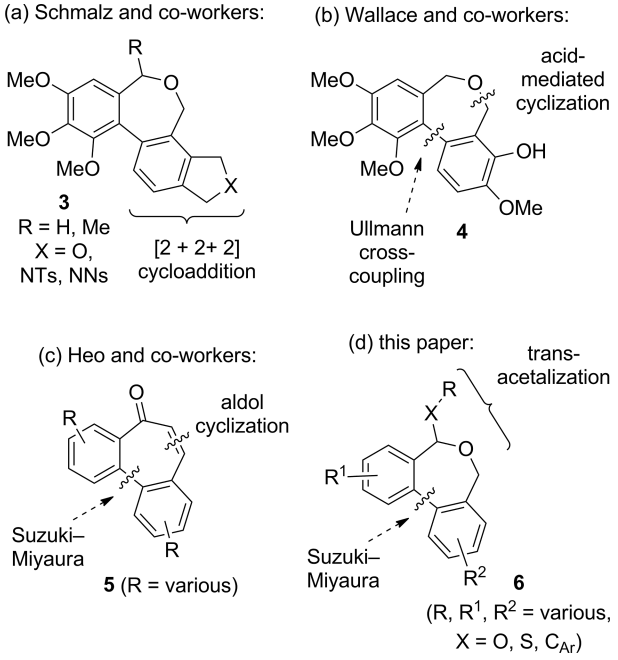


Figure 2. Representative examples of synthetic approaches resulting in allocolchicine analogues.

It is also important to note that the 7-position of the allocolchicine B-ring (numbering shown in Figure 1) has also been varied, with a number of small functional groups seemingly being tolerated in this position with respect to maintaining bioactivity.[9,15] With this in mind, and with the precedent set by Schmalz and Wallace in terms of the anticancer activity of the dibenzo[*c*,*e*]oxepine ("6-oxa") system, it was deemed valuable to look at compounds that combined both structural features (see Figure 2d). This manuscript thus describes a novel approach to the synthesis of additional 6-oxa-allocolchicinoids, i.e. 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines, readily synthesized by a strategy involving a Suzuki–Miyaura coupling reaction (compound **9** ⇒ **10** and **11**), followed by an acid-catalysed intramolecular transacetalization (**7** ⇒ **8**), as shown in the retrosynthetic analysis in Figure 3. It should be noted here that the biaryl synthesis between substituted halobenzyl alcohols and (2-formylphenyl)boronic acids was also considered, in order to avoid the protection/deprotection sequence, as this has seen some application;[12b] however, work by Van der Eycken et al. has shown that this approach can result in inseparable mixtures of biaryls due to intramolecular disproportionation reactions,[12c] and the route shown in Figure 3 was thus used.

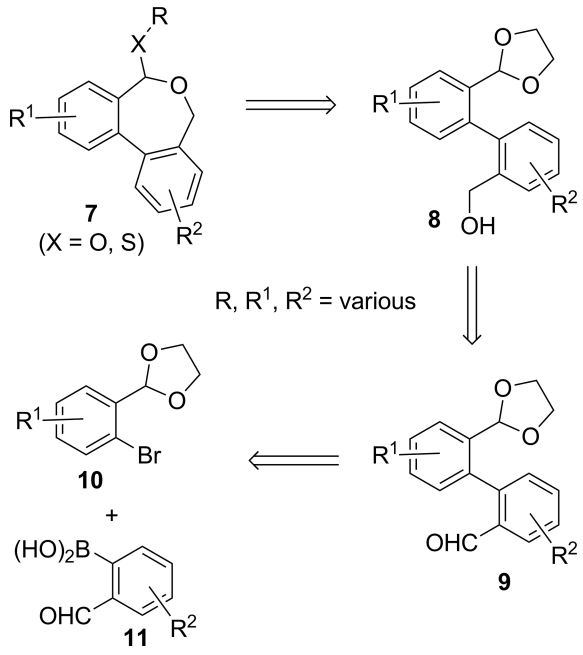
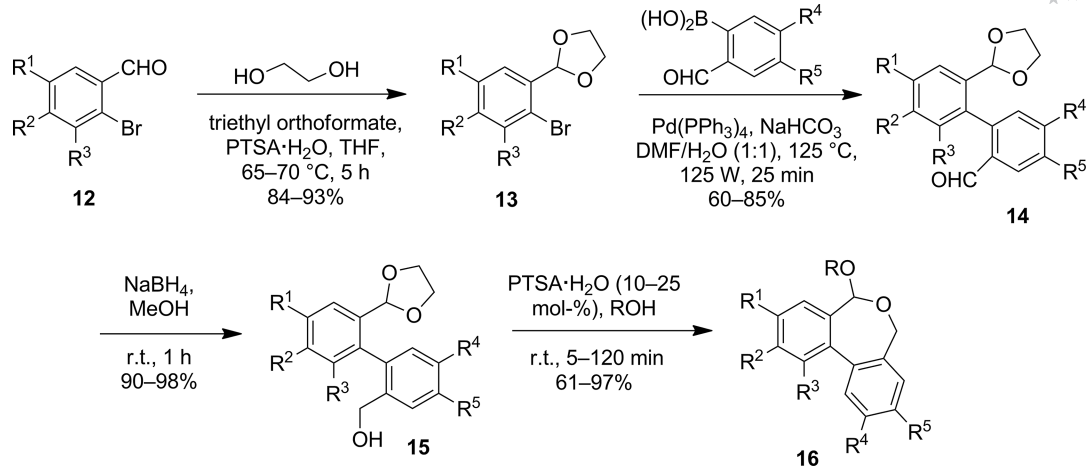


Figure 3. Key retrosynthetic disconnections resulting in 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines.

Results and Discussion

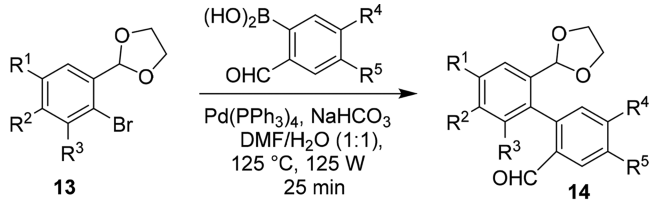
To access the desired 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]-oxepine skeleton **7**, the synthetic strategy depicted in Scheme 1 was investigated. The first synthetic task involved the conversion of a small set of five commercially available 2-bromobenzaldehydes **12**, namely 2-bromobenzaldehyde, 2-bromo-5-methoxybenzaldehyde, 2-bromo-4,5-dimethoxybenzaldehyde, 6-bromobenzo[*d*][1,3]dioxole-5-carbaldehyde and 2-bromo-3,4,5-trimethoxybenzaldehyde, into their respective 1,3-dioxolanes **13**. This was achieved by using 1,2-ethanediol (4 equiv.), triethyl orthoformate and *p*-toluenesulfonic acid monohydrate as catalyst, to provide the 1,3-dioxolanes **13** in good yields (84–93%). The important biaryl C–C bond was introduced by utilizing the Suzuki–Miyaura coupling of the five 1,3-dioxolanes using two different types of reaction conditions, under standard heating (Method A), and the other under microwave-heating conditions (Method B).[16] The yields for the biaryl products **14** were generally good, with the microwave methodology giving better yields on the whole (see Table 1 for further information and Supporting Information for structures).

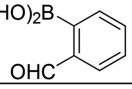
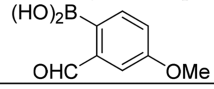
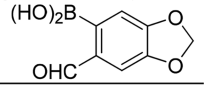
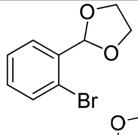
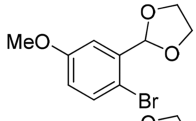
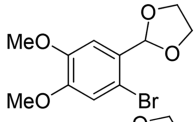
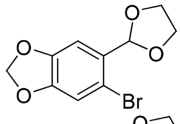
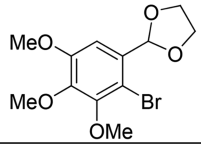
The biarylcarbaldehydes **14a**–**k** were subsequently reduced to their benzyl alcohols **15a**–**k** in excellent yields (>90%) by using sodium borohydride as the reductant. The next step involved the critical transacetalization to afford the ring-closed 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine products **16**. To achieve this, the biaryl compounds **15** were subjected to a substoichiometric amount of *p*-toluenesulfonic acid (PTSA) monohydrate in an alcoholic solvent to



Scheme 1. Synthesis of 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines **16**. For yields of biaryl products **14** and 5-alkoxy-5,7-dihydrodibenzo-[*c*,*e*]oxepines **16**, see Tables 1 and 2, respectively.

Table 1. Yields for the synthesis of the biaryls **14** by way of a Suzuki–Miyaura coupling protocol.



Aromatic bromides utilized	Boronic acids utilized (A, B refer to Suzuki–Miyaura coupling conditions[a])		
			
	**14a** (A 60%, B 75%)	**14b** (B 77%)	n.d.
	**14c** (A 70%, B 90%)	n.d.	n.d.
	**14d** (A 68%, B 80%)	**14e** (B 65%)	**14f** (B 60%)
	**14g** (B 86%)	**14h** (B 83%)	**14i** (B 60%)
	**14j** (A 65%, B 81%)	**14k** (B 69%)	n.d.

[a] Coupling conditions: A: aryl bromide (1 equiv.), boronic acid (1.5 equiv.), $NaHCO_3$ (3 equiv.), $Pd(PPh_3)_4$ (5 mol-%) in DMF/H_2O (1:1), 110 °C for 4–6 h under Ar; B: aryl bromide (1 equiv.), boronic acid (1.3 equiv.), $NaHCO_3$ (3 equiv.), $Pd(PPh_3)_4$ (5 mol-%) in DMF/H_2O (1:1; 2 mL), microwave heating (125 W), 125 °C for 25 min, sealed tube.

deliver the desired seven-membered ring systems in acceptable yields (see Table 2 for further information and the Supporting Information).[17] It was found that a range of alcohols could be utilized in this reaction, with the initial focus being on shorter-chain alcohols such as methanol, ethanol, *n*-propanol and *n*-butanol. To widen the scope of

Table 2. Yields for the transacetalization of biaryls **15** with various alcohols to afford 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines **16**.

15[a]	Substitution key	Compound (yield [%])[b]				
		MeOH (**a**) R = Me	EtOH (**b**) R = Et	*n*PrOH (**c**) R = *n*Pr	*n*BuOH (**d**) R = *n*Bu	Propargyl alcohol (**e**) R = CH_2CCH
a	R^1, R^2, R^3, R^4, R^5 = H	**16aa** (71)	**16ab** (74)	n.d.	**16ad** (78)	n.d.
b	R^1, R^2, R^3, R^4 = H; R^5 = OMe	**16ba** (82)	**16bb** (90)	**16bc** (86)	**16bd** (91)	**16be** (67)
c	R^2, R^3, R^4, R^5 = H; R^1 = OMe	**16ca** (83)	**16cb** (85)	n.d.	**16cd** (85)	n.d.
d	R^3, R^4, R^5 = H; R^1, R^2 = OMe	**16da** (90)	**16db** (72)	n.d.	**16dd** (84)	**16de** (83)
e	R^3, R^4 = H; R^1, R^2, R^5 = OMe	n.d.	n.d.	**16ec** (76)	n.d.	n.d.
f	R^1, R^2 = OMe; R^4, R^5 = $–OCH_2O–$; R^3 = H	n.d.	n.d.	**16fc** (85)	n.d.	n.d.
g	R^1, R^2 = OCH_2O; R^3, R^4, R^5 = H	**16ga** (72)	n.d.	**16gc** (89)	n.d.	**16ge** (81)
h	R^1, R^2 = OCH_2O; R^3, R^4 = H; R^5 = OMe	**16ha** (96)	**16hb** (84)	**16hc** (84)	**16hd** (97)	n.d.
i	R^1, R^2 = OCH_2O; R^4, R^5 = OCH_2O; R^3 = H	**16ia** (89)	n.d.	**16ic** (63)	**16id** (78)	n.d.

[a] Use of substrate **15j** resulted in multiple products, which could not be readily separated by chromatography. [b] After chromatographic purification.

this approach, other alcohols, such as benzyl alcohol, allyl alcohol and propargyl alcohol, were also used in the transacetalization to give the desired cyclized products **16** in acceptable yields. The reason for utilizing the propargyl alcohol to obtain compounds **16be**, **16de** and **16ge**, was to investigate the possibility of utilizing this alkyne "handle" for possible extension by way of a click reaction, as has been done by several other research groups.[18] In terms of a limitation, it was observed that when the biarylylmethanols **15** possessed a methoxy group in the "R^3" position that the ring-closure to the desired cyclized products **16** was not successful. Even when the reaction temperature was increased gently (ca. 40 °C) at best multiple inseparable products were seen by TLC analysis (of interest was that this was less of a problem when utilizing phenol and thiophenol as nucleophilic solvents – see next section).

To broaden the scope of alcohols that could be utilized in the transacetalization of the biaryls **15**, compounds **16cf** and **16dg** were both obtained in reasonable yields when using benzyl and allyl alcohol, respectively, demonstrating that the synthetic method could be used to prepare 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines **16** with a wider variety of substituents at the alkoxy portion of the molecule (structures shown in Figure 4).

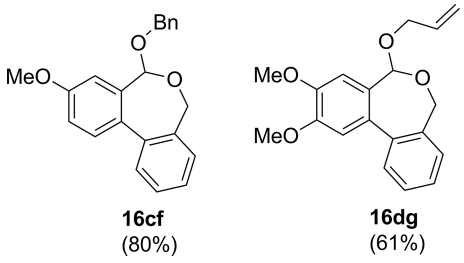


Figure 4. Further examples of 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]-oxepines synthesized, with isolated yields in parentheses.

The transacetalization reaction was also performed in a mixed THF/water medium to afford the hemiacetal 5,7-dihydrodibenzo[*c*,*e*]oxepin-5-ol (**16ah**; Figure 5a), which – although prone to decomposition in the deuterated solvents used – gave single crystals of a sufficient quality for an X-ray diffraction study (a previous study has shown that in solution **16ah** is in equilibrium with the corresponding benzyl alcohol/benzaldehyde – see Experimental Section for more details). The solved structure of the solid showed it clearly contained the desired seven-membered 5,7-dihydrodibenzo[*c*,*e*]oxepin-5-ol ring system as can be seen in Figure 5b.

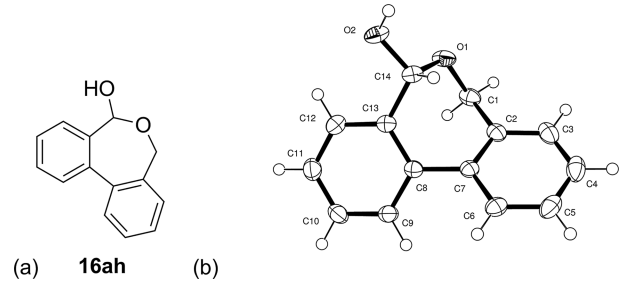
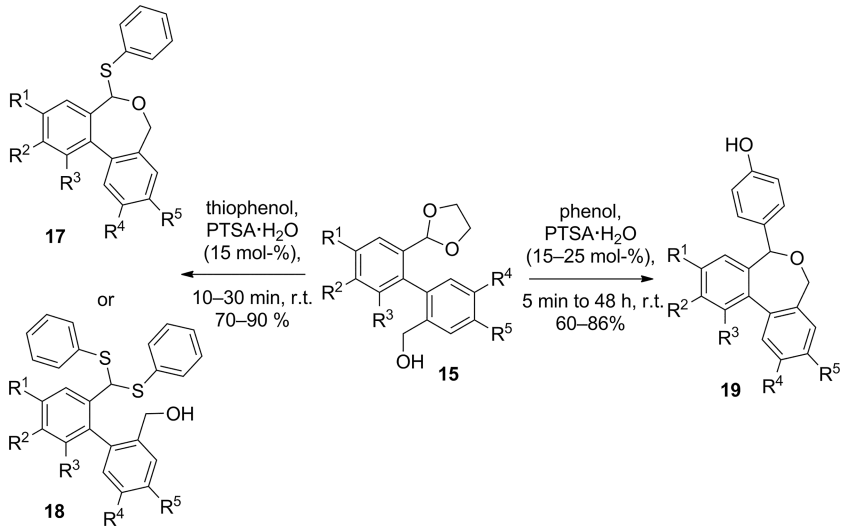


Figure 5. (a) Structure 5,7-dihydrodibenzo[*c*,*e*]oxepin-5-ol (**16ah**); (b) single-crystal X-ray structure for **16ah** (ORTEP diagram drawn at 50% probability level).

Finally, it was decided to investigate the transacetalization reaction by using phenol and the related thiophenol as the "alcohol" partners. Initial reactions of substrates **15a**–**c** with thiophenol gave products **17ai**, **17bi** and **17ci**, respectively, that had the expected incorporation of the thiophenol to give the 5-(phenylsulfanyl)-5,7-dihydrodibenzo[*c*,*e*]oxepines structure containing an O,S-acetal (Scheme 2, Table 3). However, for a number of reactions involving substrates with more electron-donating groups (for instance, **15h**, **15j** and **15k**) the NMR spectra clearly indicated the incorporation of two thiophenol groups into the final product **18** (namely **18hi**, **18ji** and **18ki**, respectively), thus showing that the S,S-actetals had been formed instead (Scheme 2, Table 3). An important clue towards the formation of these products was that the Ar*C*H(SPh)$_2$ proton for these products resonated at $\delta \approx 5.1$ ppm (see related example in ref.[19] with resonance at $\delta = 5.3$ ppm), while for the Ar*C*H(SPh)(OCH$_2$Ar) systems the proton signal was found at $\delta \approx 6.2$ ppm (further corroborated by examples in the literature; see for example ref.[20] with related resonance at $\delta = 5.69$ ppm). Examination of the ^{13}C NMR spectra also indicated the significant difference in the Ar*C*H(SPh)$_2$ vs.



Scheme 2. Synthesis of substituted 5-(phenylsulfanyl)-5,7-dihydrodibenzo[*c*,*e*]oxepines **17**, {2′-[bis(phenylsulfanyl)methyl][1,1′-biphenyl]-2-yl}methanols **18** and 4-(5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenols **19**.

Table 3. Yields for the synthesis of substituted 5-(phenylsulfanyl)-5,7-dihydrodibenzo[*c*,*e*]oxepines **17**, {2′-[bis(phenylsulfanyl)methyl][1,1′-biphenyl]-2-yl}methanols **18** and 4-(5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenols **19**.

15[a]	Substitution key	Compound (yield [%])[b] Thiophenol (**i**)	Phenol (**j**)
a	R^1, R^2, R^3, R^4, R^5 = H	**17ai** (70)	**19aj** (73)
b	R^1, R^2, R^3, R^4 = H; R^5 = OMe	**17bi** (86)	**19bj** (81)
c	R^2, R^3, R^4, R^5 = H; R^1 = OMe	**17ci** (90)	**19cj** (80)
d	R^3, R^4, R^5 = H; R^1, R^2 = OMe	n.d.	**19dj** (75)
e	R^3, R^4 = H; R^1, R^2, R^5 = OMe	n.d.	**19ej** (75)
g	R^1, R^2 = –OCH_2O–; R^3, R^4, R^5 = H	n.d.	**19gj** (86)
h	R^1, R^2 = –OCH_2O–; R^3, R^4 = H; R^5 = OMe	**18hi** (87)	**19hj** (85)
j	R^1, R^2, R^3 = OMe; R^4, R^5 = H	**18ji** (90)	**19jj** (60)
k	R^1, R^2, R^3, R^5 = OMe; R^4 = H	**18ki** (71)	**19kj** (60)

[a] Compounds **15f** and **15i** not used as substrates. [b] After chromatographic purification.

Ar*C*H(SPh)(OCH_2Ar) chemical shifts ($\delta \approx 60$ ppm for compounds **18** vs. $\delta \approx 90$ ppm for compounds **17**). In terms of rationalizing why these differences were observed, it is postulated that the presence of multiple electron-donating groups on the masked aldehyde-bearing ring decrease the electrophilicity of the acetal system required for the cyclization.

Secondly, utilization of phenol as the nucleophile gave an initially unexpected product, in which from NMR spectroscopic evaluation it looked like a C–C bond had formed, rather than the O,O-acetal. It was soon noted that examples, where phenol has reacted by way of a nucleophilic carbon atom rather than the oxygen atom of the phenol functionality, are known in the literature.[21] To confirm the structure of these products, a single-crystal X-ray experiment was performed on product **19kj**, which confirmed that C–C bond formation had occurred (Figure 6).

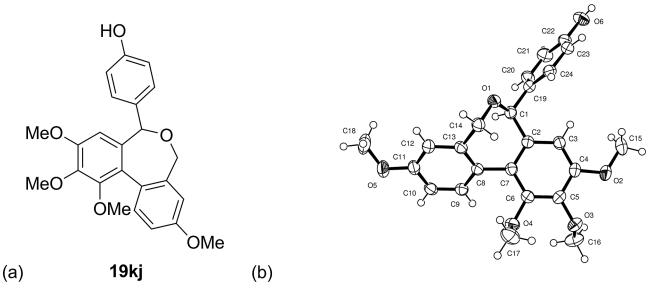


Figure 6. (a) Structure of compound **19kj**; (b) single-crystal X-ray structures for **19kj** (ORTEP diagram drawn at 50% probability level).

A number of the compounds were evaluated for their ability to attenuate the human leukemia cell-line Nalm6, namely **16be**, **16da**, **16ga**, **16ia**, **17bi**, **17ci** and **19kj**, as related compounds prepared by Schmalz and co-workers had shown interesting activities.[7a,7c–7e,9,18b] Unfortunately, the compounds only demonstrated moderate activity in terms of inhibition of cell proliferation, and compounds **16be**, **16da**, **16ga**, **16ia** and **17ci** had IC_{50} values in the range of 50–100 μM. It has been shown in previous research that the axial stereochemical configuration of colchicinoid compounds is critical in terms of their ability to slow cell growth by the inhibition of tubulin polymerization,[22] and it is possible that the compounds synthesized in this study are too flexible for the desired atropisomer to interact effectively with the tubulin binding site. In the future, it is our

aim to synthesize related compounds, which are more rigid and have less flexibility in terms of rotation around the biaryl axis of the compounds. In addition, compound **16da** was also found to be able to sensitize vincristine-resistant leukemia (Nalm6) and lymphoma (Bibo) cells to the drug vincristine. At a concentration of 5 μM of **16da** (lower than the IC_{50} value for the compound alone) and 10 nM of vincristine, over 75% of the vincristine-resistant Nalm6 cells underwent apoptosis (although higher concentrations of **16da** were required for the resistant Bibo cells; see Supporting Information). The synergistic application of cytotoxic agents is an important area of research in oncology,[23] and this interesting activity provides additional impetus for the study of these 6-oxa-allocolchicinoids.

Conclusions

In this paper, a novel synthesis of 28 6-oxa-allocolchicinoids (5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines) with varying substitution patterns has been reported. In addition, three substituted 5-(phenylsulfanyl)-5,7-dihydrodibenzo-[*c*,*e*]oxepines and nine 4-(5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenols were also synthesized. The key steps involved in the synthesis were a palladium-mediated Suzuki–Miyaura coupling to afford the intermediate biphenyl-2-carbaldehydes. After reduction of the biarylcarbaldehydes to the respective alcohols, these compounds were cyclized by way of an acid-catalyzed intramolecular transacetalization to afford the desired 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines (in addition to some related phenol and thiophenol analogues). A number of the compounds were tested for their ability to inhibit the proliferation of the human leukemia cell-line Nalm6, and – unfortunately – the compounds were only found to be active in the 50–100 μM range. However, some preliminary results, indicating that compound **16da** was able to re-sensitize vincristine-resistant cell lines to this important drug reaffirm that this class of small molecules is well worth investigating. It should thus be noted that the synthetic strategy employed to synthesize the allocolchicine analogues, readily afforded small libraries of compounds with diverse substitution patterns.

Experimental Section

General Considerations: ^1H and ^{13}C NMR spectra were recorded either with a 300 or 500 MHz spectrometer at the frequency indicated. IR spectra were recorded with Fourier transform spectrometers. Mass spectra were recorded with a Kratos MS 9/50, VG 70E MS or VG 70 SEQ mass spectrometer, a WatersAPI Q-TOF Ultima or Waters GCT Premier mass spectrometer. Melting points were determined with a standard hot-stage apparatus. All reactions were monitored by TLC carried out on 0.2 mm aluminium silica gel (60 F_{254}) pre-coated plates by using UV light. Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography. Commercially available reagents and solvents were purified and dried when necessary by conventional techniques.[24] THF and Et_2O were purified by distillation under nitrogen from sodium and benzophenone. In addition, dichloromethane was dried by distillation from calcium hydride. Unless otherwise mentioned, all other reagents were purchased from commercial sources and were used without further purification. Finally, reactions were performed under a blanket of inert gas (Ar or N_2) unless specified. In the numbering of the compounds in the manuscript, the first alphabetical letter refers to the biaryl substrate utilized and the second to the nucleophilic solvent (**a** = MeOH, **b** = EtOH, **c** = *n*PrOH, **d** = *n*BuOH, **e** = propargyl alcohol, **f** = benzyl alcohol, **g** = allyl alcohol, **h** = water, **i** = thiophenol, **j** = phenol).

Experimental Procedures

General Procedure for the Preparation of 1,3-Dioxolanes 13: 1,2-Ethanediol (4 equiv.), triethyl orthoformate (1 equiv.) and *p*-toluenesulfonic acid monohydrate (0.1 equiv.) were added to a solution of substituted 2-bromobenzaldehyde (1 equiv.) in THF (10 mL). The reaction mixture was then heated at 65–70 °C for 3–5 h and was poured into a solution of $NaHCO_3$ (10%, 5 mL). This was extracted with EtOAc (2× 30 mL), after which the combined organic layers were washed with brine and dried with Na_2SO_4, followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography using suitable solvent mixtures of EtOAc/hexane as eluent, to afford the desired 1,3-dioxolane compounds **13** as described below. The compounds were fully characterized by spectroscopy (^1H and ^{13}C NMR, IR and HRMS) and their spectra compared well to those published in the literature. The following known compounds were generated in this way: 2-(2-bromophenyl)-1,3-dioxolane (**13a**) from 2-bromobenzaldehyde (**12a**) (reaction time 3 h; eluent: 20% EtOAc/hexane mixture; yield 84%),[25] 2-(2-bromo-5-methoxyphenyl)-1,3-dioxolane (**13b**) from 2-bromo-5-methoxybenzaldehyde (**12b**) (reaction time 5 h; eluent: 20% EtOAc/hexane mixture; yield 85%),[26] 2-(2-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane (**13c**) from 2-bromo-4,5-dimethoxybenzaldehyde (**12c**) (reaction time 3 h; eluent: 20% EtOAc/hexane mixture; yield 93%),[27] 5-bromo-6-(1,3-dioxolan-2-yl)benzo[1,3]dioxole (**13d**) from 6-bromobenzo[*d*][1,3]dioxole-5-carbaldehyde (**12d**) (reaction time 3 h; eluent: 20% EtOAc/hexane mixture; yield 92%)[28] and 2-(2-bromo-3,4,5-trimethoxyphenyl)-1,3-dioxolane (**13e**) from 2-bromo-3,4,5-trimethoxybenzaldehyde (**12e**) (reaction time 3 h; eluent: 20% EtOAc/hexane mixture; yield 86%).[14]

General Procedure for the Preparation of Biphenyl-2-carbaldehydes 14 by Suzuki–Miyaura Coupling

Method A. General Procedure for Classical Suzuki–Miyaura Reaction: Aryl bromide (1 equiv.), boronic acid (1.5 equiv.), $NaHCO_3$ (3 equiv.), and $Pd(PPh_3)_4$ (5 mol-%) were suspended in a mixture of DMF/H_2O (1:1, 5 mL each) in a flame-dried flask. The mixture was heated to 110 °C under Ar for 4–6 h. After completion of the reaction (by TLC), the mixture was partitioned between EtOAc and H_2O, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, and the solvent was removed under reduced pressure to yield the crude product. This material was purified by flash silica gel column chromatography using suitable mixtures of EtOAc/hexane as eluent, to afford the desired substituted biphenyl-2-carbaldehydes **14**.

Method B. General Procedure for Microwave (MW) Assisted Suzuki–Miyaura Reaction: To a flame-dried microwave vial (10 mL), equipped with a stirring bar, were added 2-(2-bromophenyl)dioxolane **13** (1 equiv.), boronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (5 mol-%) and $NaHCO_3$ (3 equiv.) in DMF/H_2O (1:1, 2 mL) to the vial, after which it was sealed. The vial was then irradiated in a microwave reactor at 125 °C and 125 W for 25 min. After cooling

of the vessel, the reaction mass was filtered, diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography using suitable solvent mixtures of EtOAc/hexane as eluent to afford the following desired substituted biphenyl-2-carbaldehydes **14**.

2′-(1,3-Dioxolan-2-yl)biphenyl-2-carbaldehyde (14a): Reaction time 4 h; eluent: 10% EtOAc/hexane mixture; yield 60% (Method A) or 75% (Method B); spectra corresponded well to those published in the literature.[29]

2′-(1,3-Dioxolan-2-yl)-4-methoxybiphenyl-2-carbaldehyde (14b): Reaction time 4 h; eluent: 20% EtOAc/hexane mixture; yield 77% (Method A); white solid; R_f = 0.53 (EtOAc/hexane, 3:7); m.p. 65–68 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2873, 1687, 1605, 1484, 1396, 1316, 1266, 1225, 1165 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.67 (s, 1 H), 7.68 (dd, J = 7.5, 1.5 Hz, 1 H), 7.51 (d, J = 2.8 Hz, 1 H), 7.47–7.39 (m, 2 H), 7.29 (d, J = 8.4 Hz, 1 H), 7.22–7.15 (m, 2 H), 5.49 (s, 1 H), 4.02–3.91 (m, 2 H), 3.90 (s, 3 H), 3.86–3.76 (m, 2 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 191.8, 159.3, 137.3, 136.5, 136.4, 135.3, 132.4, 131.2, 128.8, 128.3, 126.9, 120.6, 109.2, 101.9, 65.3, 65.2, 55.6 ppm. MS (EI): m/z (%) = 307 (25) [M^+ + Na], 285 (100) [M^+ + H], 279 (10), 223 (30). HRMS: calcd. for $C_{17}H_{16}O_4$ [M^+ + H] 285.1136, found 285.1138.

2′-(1,3-Dioxolan-2-yl)-4′-methoxybiphenyl-2-carbaldehyde (14c): Reaction time 6 h; eluent: 10% EtOAc/hexane mixture; yield 70% (Method A) or 90% (Method B); reddish liquid; R_f = 0.46 (EtOAc/hexane, 3:7). IR (neat, film): $\tilde{\nu}_{max}$ = 2885, 1688, 1600, 1471, 1392, 1273, 1224 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.74 (s, 1 H), 8.01 (d, J = 7.6 Hz, 1 H), 7.63–6.52 (m, 1 H), 7.52 (m, 1 H), 7.36 (d, J = 7.5 Hz, 1 H), 7.23 (d, J = 2.3 Hz, 1 H), 7.14 (d, J = 8.4 Hz, 1 H), 6.97 (dd, J = 8.3, 2.4 Hz, 1 H), 5.46 (s, 1 H), 3.99–3.89 (m, 2 H), 3.88 (s, 3 H), 3.86–3.75 (m, 2 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 192.2, 159.7, 143.6, 137.3, 134.7, 133.0, 132.0, 131.7, 129.7, 127.9, 126.7, 114.7, 111.8, 101.8, 65.3, 65.2, 55.4 ppm. MS (EI): m/z (%) = 285 (20) [M^+ + H], 284 (100) [M^+]: HRMS: calcd. for $C_{17}H_{16}O_4$ [M^+ + H] 285.1127, found 285.1123.

2′-(1,3-Dioxolan-2-yl)-4′,5′-dimethoxy-1,1′-biphenyl-2-carbaldehyde (14d): Reaction time 6 h; eluent: 20% EtOAc/hexane mixture; yield 68% (Method A) or 80% (Method B); white crystalline solid; R_f = 0.33 (EtOAc/hexane, 2:3); m.p. 114–116 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2888, 1689, 1594, 1517, 1475, 1451, 1393, 1344, 1282, 1268, 1233, 1198 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.77 (s, 1 H), 8.02 (dd, J = 7.7, 1.2 Hz, 1 H), 7.65–7.57 (m, 1 H), 7.55–7.48 (m, 1 H), 7.39 (dd, J = 7.5, 0.9 Hz, 1 H), 7.19 (s, 1 H), 6.70 (s, 1 H), 5.37 (s, 1 H), 4.05–3.93 (m, 5 H), 3.87 (s, 3 H), 3.83–3.74 (m, 2 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 192.1, 149.1, 149.0, 143.5, 134.7, 133.0, 131.5, 130.1, 128.2, 128.0, 126.7, 113.4, 109.3, 101.6, 65.2, 65.1, 56.1, 56.0 ppm. MS (EI): m/z (%) = 337 (100) [M^+ + Na], 315 (18) [M^+ + H], 229 (18). HRMS: calcd. for $C_{18}H_{18}O_5$ [M^+ + H] 315.1233, found 315.1244.

2′-(1,3-Dioxolan-2-yl)-4,4′,5′-trimethoxybiphenyl-2-carbaldehyde (14e): Eluent: 30% EtOAc/hexane mixture; yield 65% (Method B), red crystalline solid; R_f = 0.56 (EtOAc/hexane, 3:2); m.p. 117–120 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2868, 1685, 1603, 1519, 1493, 1460, 1392, 1345, 1313, 1263, 1242, 1203 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.73 (s, 1 H), 7.51 (d, J = 2.8 Hz, 1 H), 7.32 (d, J = 8.4 Hz, 1 H), 7.20–7.05 (m, 2 H), 6.69 (s, 1 H), 5.37 (s, 1 H), 4.08–4.00 (m, 2 H), 3.98 (s, 3 H), 3.91 (s, 3 H), 3.87 (s, 3 H), 3.84–3.77 (m, 2 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 192.0, 159.3, 149.0, 148.9, 136.2, 135.5, 132.7, 129.8, 128.5, 120.7, 113.8 (2 C), 109.2, 101.6, 65.2, 65.1, 56.0, 55.9, 55.6 ppm. MS (EI): m/z (%) = 367 (100) [M^+ + Na], 345 (98) [M^+ + H], 255 (70). HRMS: calcd. for $C_{19}H_{20}O_6$ [M^+ + H] 345.1338, found 345.1339.

6-[2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl]benzo[1,3]dioxole-5-carbaldehyde (14f): Eluent: 20% EtOAc/hexane mixture; yield 60% (Method B); white solid; R_f = 0.39 (EtOAc/hexane, 1:1); m.p. 160–163 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 1674, 1608, 1480, 1400, 1362, 1253, 1201 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.54 (s, 1 H), 7.45 (s, 1 H), 7.18 (s, 1 H), 6.81 (s, 1 H), 6.67 (s, 1 H), 6.10 (2 × s overlapping, 2 H), 5.41 (s, 1 H), 4.11–4.02 (m, 2 H), 3.97 (s, 3 H), 3.90–3.80 (m, 5 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 190.4, 151.6, 149.1, 149.0, 147.9, 140.6, 129.8, 129.7, 128.4, 113.4, 111.0, 109.1, 105.6, 102.1, 101.4, 65.2 (2 C), 56.0, 55.9 ppm. MS (EI): m/z (%) = 359 (100) [M^+ + H]. HRMS: calcd. for $C_{19}H_{18}O_7$ [M^+ + H] 359.1131, found 359.1133.

2-[6-(1,3-Dioxolan-2-yl)benzo[1,3]dioxol-5-yl]benzaldehyde (14g): Eluent: 20% EtOAc/hexane mixture; yield 86% (Method B); light yellow solid; R_f = 0.56 (EtOAc/hexane, 2:3); m.p. 106–108 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2893, 1694, 1595, 1503, 1477, 1418, 1390, 1255, 1208 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.80 (s, 1 H), 8.02 (dd, J = 7.7, 1.2 Hz, 1 H), 7.64–7.57 (m, 1 H), 7.54–7.47 (m, 1 H), 7.36 (dd, J = 7.5, 0.9 Hz, 1 H), 7.16 (s, 1 H), 6.69 (s, 1 H), 6.05 (s, 2 H), 5.33 (s, 1 H), 4.04–3.92 (m, 2 H), 3.85–3.73 (m, 2 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 191.9, 147.9, 147.8, 143.2, 134.6, 133.1, 131.4 (2 C), 130.0, 128.1, 126.8, 110.5, 106.8, 101.6, 101.3, 65.3, 65.2 ppm. MS (EI): m/z (%) = 321(100) [M^+ + Na], 299 (98) [M^+ + H], 279 (15). HRMS: calcd. for $C_{17}H_{14}O_5$ [M^+ + H] 299.0919, found 299.0923.

2-[6-(1,3-Dioxolan-2-yl)benzo[1,3]dioxol-5-yl]-5-methoxybenzaldehyde (14h): Eluent: 20% EtOAc/hexane mixture; yield 83% (Method B); light orange solid; R_f = 0.40 (EtOAc/hexane, 3:7); m.p. 145–147 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2871, 1684, 1602, 1478, 1393, 1309, 1276, 1239 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.74 (s, 1 H), 7.49 (d, J = 2.3 Hz, 1 H), 7.28–7.25 (m, 1 H), 7.17–7.14 (m, 2 H), 6.66 (s, 1 H), 6.03 (s, 2 H), 5.32 (s, 1 H), 4.05–3.94 (m, 2 H), 3.90 (s, 3 H), 3.85–3.75 (m, 2 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 191.8, 159.3, 147.9, 147.8, 136.0, 135.5, 132.6, 131.2, 130.4, 120.8, 110.8, 109.3, 106.7, 101.6, 101.3, 65.3, 65.2, 55.6 ppm. MS (EI): m/z (%) = 351 (15) [M^+ + Na], 329 (75) [M^+ + H], 239 (100). HRMS: calcd. for $C_{18}H_{16}O_6$ [M^+ + H] 329.1025, found 329.1037.

6′-(1,3-Dioxolan-2-yl)-5,5′-bi(benzo[1,3]dioxolyl)-6-carbaldehyde (14i): Eluent: 20% EtOAc/hexane mixture; yield 60% (Method B); white solid; R_f = 0.33 (EtOAc/hexane, 3:7); m.p. 162–165 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2898, 1674, 1612, 1477, 1412, 1362, 1247 cm^{-1}. ^1H NMR (500 MHz; $CDCl_3$): δ = 9.55 (s, 1 H), 7.43 (s, 1 H), 7.13 (s, 1 H), 6.77 (d, J = 2.2 Hz, 1 H), 6.65 (s, 1 H), 6.09 (d, J = 1.1 Hz, 1 H), 6.08 (d, J = 1.1 Hz, 1 H), 6.03 (s, 2 H), 5.36 (s, 1 H), 4.07–3.98 (m, 2 H), 3.87–3.78 (m, 2 H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 190.2, 151.7, 148.03, 147.99, 147.94, 140.4, 131.0, 130.4, 129.9, 110.9, 110.6, 106.7, 105.8, 102.1, 101.6, 101.1, 65.34, 65.31 ppm. MS (EI): m/z (%) = 365 (5) [M^+ + Na], 343 (12) [M^+ + H], 253 (100). HRMS: calcd. for $C_{18}H_{14}O_7$ [M^+ + H] 343.0818, found 343.0820.

2′-(1,3-Dioxolan-2-yl)-4′,5′,6′-trimethoxy-1,1′-biphenyl-2-carbaldehyde (14j): Reaction time 6 h; eluent: 20% EtOAc/hexane mixture; yield 65% (Method A) or 81% (Method B); red crystalline solid; R_f = 0.40 (EtOAc/hexane, 2:3); m.p. 80–83 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2890, 1691, 1594, 1455, 1397, 1333, 1272, 1234, 1196 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.76 (s, 1 H), 8.03 (d, J = 7.0 Hz, 1 H), 7.61 (d, J = 6.8 Hz, 1 H), 7.52 (d, J = 6.8 Hz, 1 H), 7.35 (d, J = 6.8 Hz, 1 H), 7.05 (s, 1 H), 5.32 (s, 1 H), 3.96 (br. s, 5 H), 3.91 (s, 3 H), 3.85–3.77 (m, 2 H), 3.55 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 192.1, 153.7, 151.2, 142.7, 138.9,

134.9, 133.0, 132.0, 131.4, 128.0, 126.7, 124.5, 105.5, 101.4, 65.3, 65.2, 60.9, 60.7, 56.0 ppm. MS (EI): *m/z* (%) = 367 (15) [M^+ + Na], 345 (40) [M^+ + H], 255 (100). HRMS: calcd. for $C_{19}H_{20}O_6$ [M^+ + H] 345.1338, found 345.1335.

6′-(1,3-Dioxolan-2-yl)-2′,3′,4,4′-tetramethoxybiphenyl-2-carbaldehyde (14k): Eluent: 20% EtOAc/hexane mixture; yield 69% (Method B); red crystalline solid; R_f = 0.42 (EtOAc/hexane, 2:3); m.p. 85–88 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2941, 1682, 1596, 1456, 1390, 1335, 1308, 1281, 1230, 1195 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 9.69 (s, 1 H), 7.53 (d, *J* = 2.7 Hz, 1 H), 7.28 (d, *J* = 2.8 Hz, 1 H), 7.18 (dd, *J* = 8.4, 2.8 Hz, 1 H), 7.04 (s, 1 H), 5.32 (s, 1 H), 4.06–3.97 (m, 2 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.85–3.77 (m, 2 H), 3.54 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 192.0, 159.3, 153.6, 151.4, 142.7, 135.8, 133.2, 131.7, 131.4, 124.3, 120.6, 109.4, 105.4, 101.3, 65.3, 65.2, 60.9, 60.7, 56.0, 55.5 ppm. MS (EI): *m/z* (%) = 397 (65) [M^+ + Na], 376 (15), 375 (100) [M^+ + H]. HRMS: calcd. for $C_{20}H_{22}O_7$ [M^+ + H] 375.1444, found 375.1449.

General Procedure for the Preparation of Benzyl Alcohols 15 by Reduction of Biphenyl-2-carbaldehydes 14: $NaBH_4$ (1.5 equiv.) was added to a solution of aldehyde **14** (1 equiv.) in MeOH (20 mL), at 0 °C with stirring and under Ar. The reaction mixture was then stirred at room temp. for 1 h. After completion of the reaction (by TLC), the reaction mixture was concentrated under reduced pressure, diluted with H_2O and extracted with EtOAc. The organic layer was then washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure to give the desired alcohols **16** in a crude form. ^1H NMR spectroscopy indicated that these compounds were essentially pure, and they were used as such in the next step without additional purification (yields below given after removal of solvent under vacuum and further drying under high vacuum).

[2′-(1,3-Dioxolan-2-yl)biphenyl-2-yl]methanol (15a): Yield 96%; colourless liquid; R_f = 0.35 (EtOAc/hexane, 2:3). IR (neat, film): $\tilde{\nu}_{max}$ = 3405, 2885, 1474, 1443, 1393, 1203 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.67–7.64 (m, 1 H), 7.53 (d, *J* = 7.5 Hz, 1 H), 7.43–7.37 (m, 3 H), 7.33–7.28 (m, 1 H), 7.20–7.13 (m, 2 H), 5.51 (s, 1 H), 4.35–4.23 (m, 2 H), 3.98–3.90 (m, 2 H), 3.85–3.76 (m, 2 H), 3.17–3.09 (m, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 140.2, 139.5, 138.8, 135.1, 130.0, 129.8, 129.3, 129.0, 128.2, 127.9, 127.0, 126.7, 101.9, 65.6, 65.0, 62.7 ppm. MS (EI): *m/z* (%) = 279 (18) [M^+ + Na], 242 (85), 224 (100). HRMS: calcd. for $C_{16}H_{16}O_3$ [M^+ + Na] 279.0997, found 279.0997.

[2′-(1,3-Dioxolan-2-yl)-4-methoxybiphenyl-2-yl]methanol (15b): Yield 94%; white solid; R_f = 0.33 (EtOAc/hexane, 3:7); m.p. 66–68 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3476, 2898, 1606, 1463, 1428, 1397, 1303, 1230, 1159 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.66–7.63 (m, 1 H), 7.44–7.34 (m, 2 H), 7.14–7.08 (m, 3 H), 6.85 (dd, *J* = 8.4, 2.6 Hz, 1 H), 5.51 (s, 1 H), 4.33–4.20 (m, 2 H), 4.03–3.93 (m, 2 H), 3.85 (s, 3 H), 3.84–3.77 (m, 2 H), 3.16–3.09 (m, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.4, 140.9, 140.0, 135.5, 131.0, 130.8, 130.5, 129.0, 127.8, 126.6, 113.7, 113.1, 101.8, 65.6, 65.0, 62.8, 55.3 ppm. MS (EI): *m/z* (%) = 309 (15) [M^+ + Na], 225 (100), 197 (65). HRMS: calcd. for $C_{17}H_{18}O_4$ [M^+ + H] 309.1103, found 309.1106.

[2′-(1,3-Dioxolan-2-yl)-4′-methoxybiphenyl-2-yl]methanol (15c): Yield 98%; colourless liquid; R_f = 0.25 (EtOAc/hexane, 3:7). IR (neat, film): $\tilde{\nu}_{max}$ = 2865, 1608, 1505, 1480, 1453, 1312, 1267, 1231, 1194 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.52–7.46 (m, 3 H), 7.43–7.29 (m, 2 H), 7.05–7.03 (m, 2 H), 5.52 (s, 1 H), 4.48 (s, 2 H), 3.88 (s, 3 H), 3.79–3.69 (m, 2 H), 3.55–3.46 (m, 2 H), 1.92 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.5, 141.2, 136.9, 135.9, 130.8, 130.0, 129.1, 128.5, 127.4, 126.9, 114.8, 113.2, 102.6, 69.6, 67.1, 61.8, 55.5 ppm. MS (EI): *m/z* (%) = 287 (20) [M^+ + H]. HRMS: calcd. for $C_{17}H_{17}O_4$ [M^+] 285.1127, found 287.1129.

[2′-(1,3-Dioxolan-2-yl)-4′,5′-dimethoxy-1,1′-biphenyl-2-yl]methanol (15d): Yield 98%; white solid; R_f = 0.41 (EtOAc/hexane, 3:2); m.p. 100–103 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3539, 2885, 1608, 1517, 1445, 1402, 1345, 1234, 1206 cm^{-1}. ^1H NMR (500 MHz; CD_3OD, OH signal not observed): δ = 7.55 (d, *J* = 7.7 Hz, 1 H), 7.40–7.36 (m, 1 H), 7.29–7.25 (m, 1 H), 7.17 (s, 1 H), 7.14 (d, *J* = 7.5 Hz, 1 H), 6.73 (s, 1 H), 5.27 (s, 1 H), 4.39 (d, *J* = 13.2 Hz, 1 H), 4.33 (d, *J* = 13.2 Hz, 1 H), 4.02–3.98 (m, 2 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.76 (t, *J* = 4.8 Hz, 2 H) ppm. ^{13}C NMR (125 MHz; CD_3OD): δ = 150.7, 149.9, 140.9, 139.4, 134.7, 131.4, 128.9, 128.8, 128.5, 127.7, 114.2, 111.0, 102.7, 66.3, 66.2, 62.9, 56.5, 56.4 ppm. MS (EI): *m/z* (%) = 339 (30) [M^+ + Na], 317 (5) [M^+ + H], 255 (100), 227 (85). HRMS: calcd. for $C_{18}H_{20}O_5$ [M^+ + H] 317.1389, found 317.1387.

[2′-(1,3-Dioxolan-2-yl)-4,4′,5′-trimethoxybiphenyl-2-yl]methanol (15e): Yield 92%; white solid; R_f = 0.30 (EtOAc/hexane, 3:2); m.p. 118–121 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3494, 2890, 1606, 1520, 1493, 1456, 1401, 1345, 1295, 1264, 1237, 1203 cm^{-1}. ^1H NMR (500 MHz; CD_3OD, OH signal not observed): δ = 7.15 (s, 1 H), 7.13 (d, *J* = 2.7 Hz, 1 H), 7.05 (d, *J* = 8.3 Hz, 1 H), 6.83 (dd, *J* = 8.3, 2.7 Hz, 1 H), 6.70 (s, 1 H), 5.27 (s, 1 H), 4.35 (d, *J* = 13.5 Hz, 1 H), 4.29 (d, *J* = 13.5 Hz, 1 H), 4.03–4.00 (m, 2 H), 3.86 (s, 3 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.77 (td, *J* = 4.8, 1.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz; CD_3OD): δ = 160.9, 150.7, 149.8, 142.4, 134.6, 132.4, 131.4, 129.1, 114.5, 113.5, 113.0, 111.0, 102.7, 66.3, 66.2, 62.9, 56.5, 56.4, 55.7 ppm. MS (EI): *m/z* (%) = 369 (65) [M^+ + Na], 347 (10) [M^+ + H], 285 (100), 257 (40). HRMS: calcd. for $C_{19}H_{22}O_6$ [M^+ + H] 347.1495, found 347.1493.

{6-[2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)]benzo[1,3]dioxol-5-yl}methanol (15f): Yield 92%; white solid; R_f = 0.24 (EtOAc/hexane, 3:2); m.p. 58–62 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3421, 2886, 1606, 1502, 1481, 1399, 1244, 1206 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.14 (s, 1 H), 7.00 (s, 1 H), 6.67 (s, 1 H), 6.62 (s, 1 H), 5.99 (s, 2 H), 5.43 (s, 1 H), 4.21–4.01 (m, 4 H), 3.95 (s, 3 H), 3.93–3.87 (m, 2 H), 3.85 (s, 3 H), 3.24–3.12 (m, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 149.2, 148.6, 147.4, 146.5, 134.0, 132.9, 131.9, 127.2, 112.8, 109.8, 109.4, 108.7, 101.4, 101.2, 65.5, 64.9, 62.4, 56.0, 55.9 ppm. MS (EI): *m/z* (%) = 383 (100) [M^+ + Na]. HRMS: calcd. for $C_{19}H_{20}O_7$ [M^+ + Na] 383.1107, found 383.1108.

{2-[6-(1,3-Dioxolan-2-yl)benzo[1,3]dioxol-5-yl]phenyl}methanol (15g): Yield 91%; white solid; R_f = 0.30 (EtOAc/hexane, 2:3); m.p. 117–120 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3450, 2890, 1507, 1481, 1410, 1392, 1318, 1245 cm^{-1}. ^1H NMR (300 MHz; CD_3OD, OH signal not observed): δ = 7.54 (d, *J* = 7.6 Hz, 1 H), 7.41–7.32 (m, 1 H), 7.30–7.21 (m, 1 H), 7.11 (d, *J* = 6.7 Hz, 1 H), 7.05 (s, 1 H), 6.60 (s, 1 H), 5.99 (s, 2 H), 5.21 (s, 1 H), 4.39 (d, *J* = 13.4 Hz, 1 H), 4.32 (d, *J* = 13.4 Hz, 1 H), 4.01–3.97 (m, 2 H), 3.76–3.71 (m, 2 H) ppm. ^{13}C NMR (75 MHz; CD_3OD): δ = 149.4, 148.7, 140.9, 139.2, 135.7, 131.3, 130.3, 128.9, 128.3, 127.7, 110.5, 107.5, 102.8, 102.4, 66.2 (2 C), 62.8 ppm. MS (EI): *m/z* (%) = 301 (2) [M^+ + H], 239 (100), 211 (35), 181 (20). HRMS: calcd. for $C_{17}H_{16}O_5$ [M^+ + H] 301.1067, found 301.1070.

{2-[6-(1,3-Dioxolan-2-yl)benzo[1,3]dioxol-5-yl]-5-methoxyphenyl}methanol (15h): Yield 90%; white solid; R_f = 0.37 (EtOAc/hexane, 1:1); m.p. 162–165 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3420, 1608, 1480, 1409, 1236, 1156 cm^{-1}. ^1H NMR (500 MHz; CD_3OD, OH signal not observed): δ = 7.12 (d, *J* = 2.6 Hz, 1 H), 7.03 (s, 1 H),

7.01 (s, 1 H), 6.82 (dd, J = 8.4, 2.7 Hz, 1 H), 6.57 (s, 1 H), 5.99 (s, 1 H), 5.98 (s, 1 H), 5.22 (s, 1 H), 4.34 (d, J = 13.6 Hz, 1 H), 4.29 (d, J = 13.6 Hz, 1 H), 4.02–3.99 (m, 2 H), 3.83 (s, 3 H), 3.77–3.75 (m, 2 H) ppm. ^{13}C NMR (125 MHz; CD_3OD): δ = 161.0, 149.4, 148.6, 142.5, 135.6, 132.4, 131.3, 130.7, 113.4, 113.0, 110.9, 107.5, 102.8, 102.5, 66.3 (2 C), 62.9, 55.7 ppm. MS (EI): m/z (%) = 353 (10) [M^+ + Na], 331 (2) [M^+ + H], 269 (100), 241 (60), 211 (20). HRMS: calcd. for $C_{18}H_{18}O_6$ [M^+ + H] 331.1182, found 331.1188.

[6′-(1,3-Dioxolan-2-yl)-5,5′-bi(benzo[1,3]dioxolyl)-6-yl]methanol (15i): Yield 92%; white solid; R_f = 0.57 (EtOAc/hexane, 3:2); m.p. 168–170 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3431, 2903, 1617, 1503, 1476, 1413, 1394, 1326, 1245, 1212, 1182 cm^{-1}. ^{1}H NMR (500 MHz; CD_3OD, OH signal not observed): δ = 7.03 (s, 1 H), 6.99 (d, J = 5.2 Hz, 1 H), 6.59–6.57 (m, 2 H), 6.00–5.97 (m, 2 H), 5.96–5.95 (m, 2 H), 5.27 (s, 1 H), 4.26–4.18 (m, 2 H), 4.05–4.01 (m, 2 H), 3.79–3.77 (m, 2 H) ppm. ^{13}C NMR (125 MHz; CD_3OD): δ = 149.4, 148.9, 148.7, 146.6, 135.5, 135.8, 132.6, 130.8, 111.3, 110.9, 108.7, 107.4, 102.8, 102.6, 102.4, 66.3 (2 C), 62.6 ppm. MS (EI): m/z (%) = 367 (5) [M^+ + Na], 283 (25), 255 (100), 225 (15). HRMS: calcd. for $C_{18}H_{16}O_7$ [M^+ + Na] 367.0795, found 367.0794.

[6′-(1,3-Dioxolan-2-yl)-2′,3′,4′-trimethoxy-1,1′-biphenyl-2-yl]methanol (15j): Yield 95%; white solid; R_f = 0.40 (EtOAc/hexane, 3:2); m.p. 93–96 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3478, 2937, 1597, 1455, 1392, 1333, 1272, 1227, 1192 cm^{-1}. ^{1}H NMR (500 MHz; CD_3OD, OH signal not observed): δ = 7.56 (d, J = 7.7 Hz, 1 H), 7.42–7.35 (m, 1 H), 7.30–7.24 (m, 1 H), 7.12 (d, J = 7.5 Hz, 1 H), 7.05 (s, 1 H), 5.22 (s, 1 H), 4.34 (d, J = 13.8 Hz, 1 H), 4.31 (d, J = 13.8 Hz, 1 H) 4.01–3.92 (m, 2 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.75–3.73 (m, 2 H), 3.51 (s, 3 H) ppm. ^{13}C NMR (125 MHz; CD_3OD): δ = 154.5, 151.9, 144.3, 141.9, 134.5, 132.5, 131.9, 128.9, 128.8, 127.6, 127.4, 107.2, 102.4, 66.3, 66.2, 63.1, 61.4, 61.3, 56.6 ppm. MS (EI): m/z (%) = 367 (40) [M^+ + Na], 347 (5) [M^+ + H], 285 (85), 257 (100), 255 (30), 226 (20). HRMS: calcd. for $C_{19}H_{22}O_6$ [M^+ + H] 347.1494, found 347.1488.

[6′-(1,3-Dioxolan-2-yl)-2′,3′,4,4′-tetramethoxybiphenyl-2-yl]methanol (15k): Yield 96%; white solid; R_f = 0.37 (EtOAc/hexane, 3:2); m.p. 128–130 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3445, 2882, 1596, 1483, 1403, 1383, 1334, 1272, 1251, 1192 cm^{-1}. ^{1}H NMR (500 MHz; CD_3OD): δ = 7.14 (d, J = 1.8 Hz, 1 H), 7.05–7.00 (m, 2 H), 6.83 (dd, J = 8.3, 2.2 Hz, 1 H), 5.23 (s, 1 H), 4.31 (d, J = 13.9 Hz, 1 H), 4.26 (d, J = 13.9 Hz, 1 H), 4.03–3.95 (m, 2 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.77–3.74 (m, 2 H), 3.50 (s, 3 H) ppm. ^{13}C NMR (125 MHz; CD_3OD, OH signal not observed): δ = 163.5, 156.9, 154.7, 146.8, 145.9, 135.5, 135.4, 131.1, 128.8, 115.3, 115.2, 109.6, 104.9, 68.8, 68.7, 65.6, 64.0, 63.9, 59.1, 58.2 ppm. MS (EI): m/z (%) = 399 (100) [M^+ + Na], 377 (5) [M^+ + H], 359 (12). HRMS: calcd. for $C_{20}H_{24}O_7$ [M^+ + Na] 399.1420, found 399.1424.

General Procedure for the Preparation of 5-Alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines 16: To a solution of the substituted benzyl alcohol **15** (0.7 mmol) in the alkanol (5 mL) was added *p*-toluenesulfonic acid monohydrate (15–25 mol-%) at room temp. The reaction mixture was then stirred at this temperature for 5–120 min until the reaction was deemed complete (TLC). The solution was then concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with Na_2CO_3 solution (20 mL, 10%), followed by brine (20 mL), after which they were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography using suitable solvent mixture of EtOAc/hexane as eluent to afford the desired 5-alkoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines.

5-Methoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16aa): Reaction solvent: MeOH; PTSA·H_2O (15 mol-%); reaction time 5 min; eluent: 5% EtOAc/hexane mixture; yield 71%; white solid; R_f = 0.51 (EtOAc/hexane, 1:4); m.p. 50–53 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2879, 1451, 1388, 1368, 1200 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.58–7.32 (m, 8 H), 5.41 (s, 1 H), 4.50–4.42 (m, 2 H), 3.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 141.1, 138.5, 136.3, 135.9, 129.2, 129.0, 128.6, 128.5, 128.0, 127.8, 127.7, 127.2, 103.2, 66.8, 55.4 ppm. MS (EI): m/z (%) = 249 (85) [M^+ + Na], 229 (60), 195 (100). HRMS: calcd. for $C_{15}H_{14}O_2$ [M^+ + Na] 249.0891, found 249.0901.

5-Ethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16ab): Reaction solvent EtOH; PTSA·H_2O (15 mol-%); reaction time: 5 min; eluent: 5% EtOAc/hexane mixture; yield 74%; white solid; R_f = 0.54 (EtOAc/hexane, 1:4); m.p. 40–42·C. IR (neat, film): $\tilde{\nu}_{max}$ = 2973, 1452, 1390, 1368, 1348, 1202 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.58–7.32 (m, 8 H), 5.49 (s, 1 H), 4.48 (d, J = 11.7 Hz, 1 H), 4.42 (d, J = 11.7 Hz, 1 H), 3.75 (dq, J = 9.4, 7.0 Hz, 1 H), 3.40 (dq, J = 9.4, 7.0 Hz, 1 H), 1.00 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 141.1, 138.5, 136.3, 136.1, 129.1, 128.8, 128.5, 128.4, 128.0, 127.7, 127.3, 127.2, 101.1, 66.7, 63.1, 15.0 ppm. MS (EI): m/z (%) = 279 (100) [M^+], 263 (30) [M^+ + Na]. HRMS: calcd. for $C_{16}H_{16}O_2$ [M^+ + Na] 263.1048, found 263.1059.

5-Butoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16ad): Reaction solvent *n*BuOH; PTSA·H_2O (15 mol-%); reaction time: 60 min; eluent: 5% EtOAc/hexane mixture; yield 78%; colourless liquid; R_f = 0.57 (EtOAc/hexane, 1:4). IR (neat, film): $\tilde{\nu}_{max}$ = 2865, 1604, 1480, 1452, 1377, 1279, 1199 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.55–7.31 (m, 8 H), 5.48 (s, 1 H), 4.45 (m, 2 H), 3.70 (dt, J = 9.3, 6.7 Hz, 1 H), 3.32 (dt, J = 9.3, 6.2 Hz, 1 H), 1.40–1.31 (m, 2 H), 1.10–0.97 (m, 2 H), 0.75 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 141.2, 138.6, 136.4, 136.3, 129.1, 128.8, 128.5, 128.4, 127.9, 127.7, 127.5, 127.2, 101.7, 67.5, 66.8, 31.6, 19.0, 13.8 ppm. MS (EI): m/z (%) = 291 (100) [M^+ + Na], 233 (10), 295 (10), 258 (8). HRMS: calcd. for $C_{18}H_{20}O_2$ [M^+ + Na] 291.1361, found 291.1374.

5,7-Dihydrodibenzo[*c*,*e*]oxepin-5-ol (16ah): Reaction solvent: H_2O and THF, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 30% EtOAc/hexane mixture; yield 90%; white solid; R_f = 0.49 (EtOAc/hexane, 2:3); m.p. 94–96 C. IR (neat, film): $\tilde{\nu}_{max}$ = 3408, 2966, 1564, 1447, 1368, 1246, 1195 cm^{-1}. ^{1}H NMR: In our hands compound **16ah** was not very stable in $CDCl_3$, although this compound has been characterized before by Tamiya et al. who observed that **16ah** was in equilibrium with the corresponding ring-opened benzyl alcohol/benzaldehyde.[30] MS (EI): m/z (%) = 235 (100) [M^+ + Na], 229 (8), 195 (15). HRMS: calcd. for $C_{14}H_{12}O_2$ [M^+ + Na] 235.0735, found 235.0742. X-ray crystal structure details: Crystallized from EtOAc/hexane, formula: $C_{14}H_{12}O_2$, M = 212.24, colour/shape of crystal: white/needle, crystal size: 0.49 × 0.24 × 0.10 mm, a = 12.8876(4) Å, b = 4.72220(10) Å, c = 17.3673(5) Å, V = 1052.47(5) Å^3, β = 95.270(2)°, $\rho_{calcd.}$ = 1.339 Mg/m^3, μ = 0.089 mm^{-1}, F(000) = 448, Z = 4, T = 173(2) K, 13187 reflections collected, 2535 [R(int) = 0.0685] independent reflections, θ_{max} = 27.99°, 149 refined parameters, maximum residual electron density: 0.262 and –0.190 e Å^{-3}, $R1$ = 0.0510, $wR2$ = 0.1111. CCDC-1024803 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3,7-Dimethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16ba): Reaction solvent MeOH; PTSA·H_2O (15 mol-%); reaction time: 20 min; eluent: 5% EtOAc/hexane mixture; yield 82%; white solid; R_f = 0.58

(EtOAc/hexane, 3:7); m.p. 66–68 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2835, 1609, 1507, 1453, 1384, 1314, 1266, 1231 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.52–7.44 (m, 4 H), 7.41–7.35 (m, 1 H), 7.00 (dd, J = 8.4, 2.6 Hz, 1 H), 6.95 (d, J = 2.6 Hz, 1 H), 5.39 (s, 1 H), 4.46 (d, J = 11.7 Hz, 1 H), 4.41 (d, J = 11.7 Hz, 1 H), 3.87 (s, 3 H), 3.33 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.3, 138.2, 137.6, 135.5, 133.4, 129.1, 128.3, 128.2, 127.6, 127.4, 114.2, 114.0, 103.2, 67.0, 55.5, 55.4 ppm. MS (EI): *m*/*z* (%) = 279 (2) [M^+ + Na], 225 (100), 197 (60). HRMS: calcd. for $C_{16}H_{16}O_3$ [M^+ + Na] 279.0997, found 279.1006.

7-Ethoxy-3-methoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16bb): Reaction solvent: EtOH, PTSA·H_2O (15 mol-%); reaction time: 60 min; eluent: 5% EtOAc/hexane mixture; yield 90%; colourless viscous liquid. R_f = 0.68 (EtOAc/hexane, 3:7). IR (neat, film): $\tilde{\nu}_{max}$ = 2865, 1607, 1505, 1451, 1312, 1263, 1229 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.57 (d, J = 7.3 Hz, 1 H), 7.48–7.42 (m, 3 H), 7.40–7.35 (m, 1 H), 6.99 (dd, J = 8.4, 2.6 Hz, 1 H), 6.95 (d, J = 2.6 Hz, 1 H), 5.46 (s, 1 H), 4.45 (d, J = 11.7 Hz, 1 H), 4.39 (d, J = 11.7 Hz, 1 H), 3.86 (s, 3 H), 3.80–3.73 (m, 1 H), 3.42 (dq, J = 9.4, 7.0 Hz, 1 H), 1.05 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.3, 138.3, 137.5, 135.8, 133.5, 129.0, 128.4, 128.1, 127.4, 127.3, 114.1, 114.0, 101.1, 66.9, 63.4, 55.4, 15.1 ppm. MS (EI): *m*/*z* (%) = 489 (100), 293 (4) [M^+ + Na], 225 (8). HRMS: calcd. for $C_{17}H_{18}O_3$ [M^+ + Na] 293.1154, found 293.1161.

3-Methoxy-7-propoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16bc): Reaction solvent: *n*PrOH, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 10% EtOAc/hexane mixture; yield 86%; white solid; R_f = 0.70 (EtOAc/hexane, 3:7); m.p. 84–86 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2865, 1604, 1479, 1459, 1313, 1263, 1228 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.55 (d, J = 7.4 Hz, 1 H), 7.48–7.42 (m, 3 H), 7.40–7.35 (m, 1 H), 7.01–6.95 (m, 2 H), 5.46 (s, 1 H), 4.45 (d, J = 11.7 Hz, 1 H), 4.37 (d, J = 11.7 Hz, 1 H), 3.86 (s, 3 H), 3.68 (dt, J = 9.2, 6.7 Hz, 1 H), 3.31 (dt, J = 9.2, 6.3 Hz, 1 H), 1.50–1.39 (m, 2 H), 0.69 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.3, 138.3, 137.6, 135.8, 133.6, 129.0, 128.4, 128.1, 127.4, 127.3, 114.2, 114.1, 101.6, 69.6, 66.9, 55.4, 22.8, 10.4 ppm. MS (EI): *m*/*z* (%) = 307 (2) [M^+ + Na], 225 (100), 197 (65). HRMS: calcd. for $C_{18}H_{20}O_3$ [M^+ + Na] 307.1310, found 307.1320.

7-Butoxy-3-methoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16bd): Reaction solvent: *n*BuOH, PTSA·H_2O (15 mol-%); reaction time: 20 min; eluent: 5% EtOAc/hexane mixture; yield 91%; colourless viscous liquid; R_f = 0.66 (EtOAc/hexane, 3:7). IR (neat, film): $\tilde{\nu}_{max}$ = 2955, 1607, 1506, 1452, 1312, 1263, 1229 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.54 (d, J = 7.4 Hz, 1 H), 7.47–7.39 (m, 3 H), 7.40–7.35 (m, 1 H), 6.99 (dd, J = 8.4, 2.6 Hz, 1 H), 6.95 (d, J = 2.5 Hz, 1 H), 5.46 (s, 1 H), 4.45 (d, J = 11.7 Hz, 1 H), 4.39 (d, J = 11.7 Hz, 1 H), 3.86 (s, 3 H), 3.73 (dt, J = 9.3, 6.7 Hz, 1 H), 3.34 (dt, J = 9.3, 6.2 Hz, 1 H), 1.40 (dt, J = 7.3, 6.6 Hz, 2 H), 1.09 (dq, J = 8.1, 7.3 Hz, 2 H), 0.78 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.3, 138.3, 137.6, 135.9, 133.6, 129.0, 128.4, 128.1, 127.4, 127.3, 114.2, 114.0, 101.7, 67.6, 66.9, 55.4, 31.7, 19.0, 13.8 ppm. MS (EI): *m*/*z* (%) = 337 (100), 321 (20) [M^+ + Na], 297 (4) [M^+ – 1], 263 (8), 225 (10). HRMS: calcd. for $C_{19}H_{22}O_3$ [M^+ + Na] 321.1467, found 321.1482.

3-Methoxy-7-(prop-2-ynyl)oxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16be): Reaction solvent: propargyl alcohol, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 10% EtOAc/hexane mixture; yield 67%; white solid; R_f = 0.61 (EtOAc/hexane, 3:7); m.p. 61–63 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3272, 2851, 1606, 1510, 1484, 1463, 1400, 1313, 1265, 1247, 1229 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.5–7.46 (m, 4 H), 7.40–7.34 (m, 1 H), 6.98 (dd, J = 8.4, 2.6 Hz, 1 H), 6.92 (d, J = 2.6 Hz, 1 H), 5.79 (s, 1 H), 4.48–4.40 (m, 2 H), 4.26 (dd, J = 15.9, 2.4 Hz, 1 H), 4.06 (dd, J = 15.9, 2.4 Hz, 1 H), 3.85 (s, 3 H), 2.33 (t, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.2, 138.5, 137.6, 134.9, 133.5, 129.4, 128.5, 128.4, 128.3, 127.4, 114.2, 114.0, 100.4, 79.4, 74.3, 67.1, 55.4, 53.9 ppm. MS (EI): *m*/*z* (%) = 303 (3) [M^+ + Na], 225 (100), 197 (65). HRMS: calcd. for $C_{18}H_{16}O_3$ [M^+ + Na] 303.0997, found 303.1008.

3,5-Dimethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16ca): Reaction solvent: MeOH, PTSA·H_2O (15 mol-%); reaction time: 5 min; eluent: 10% EtOAc/hexane mixture; yield 83%; white solid; R_f = 0.43 (EtOAc/hexane, 1:4); m.p. 70–73 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2874, 1603, 1500, 1477, 1450, 1384, 1307, 1275, 1228, 1201 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.52–7.41 (m, 3 H), 7.39–7.29 (m, 2 H), 7.11 (d, J = 2.4 Hz, 1 H), 7.02 (dd, J = 8.4, 2.5 Hz, 1 H), 5.33 (s, 1 H), 4.49 (d, J = 11.7 Hz, 1 H), 4.42 (d, J = 11.7 Hz, 1 H) 3.87 (s, 3 H), 3.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.5, 140.8, 137.2, 135.9, 130.8, 129.7, 128.9, 128.5, 127.3, 127.0, 115.0, 112.4, 102.6, 67.0, 55.6, 55.5 ppm. MS (EI): *m*/*z* (%) = 257 (20) [M^+ + H]. 256, (100) [M^+]. HRMS: calcd. for $C_{16}H_{16}O_3$ [M^+] 256.1099, found 256.1002.

5-Ethoxy-3-methoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16cb): Reaction solvent: EtOH, PTSA·H_2O (15 mol-%); reaction time: 5 min; eluent: 10% EtOAc/hexane mixture; (0.160 g, 0.593 mmol), yield 85%; colourless liquid. R_f = 0.50 (EtOAc/hexane, 1:4). IR (neat, film): $\tilde{\nu}_{max}$ =2862, 1607, 1504, 1479, 1453, 1310, 1266, 1231, 1193 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.51–7.41 (m, 3 H), 7.38–7.29 (m, 2 H), 7.17 (d, J = 2.5 Hz, 1 H), 7.02 (dd, J = 8.4, 2.5 Hz, 1 H), 5.41 (s, 1 H), 4.49 (d, J = 11.7 Hz, 1 H), 4.41 (d, J = 11.7 Hz, 1 H), 3.88 (s, 3 H), 3.77 (dq, J = 9.0, 7.1 Hz, 1 H), 3.43 (dq, J = 9.0, 7.1 Hz, 1 H), 1.04 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.5, 140.8, 137.5, 135.9, 130.9, 129.6, 128.8, 128.5, 127.2, 127.0, 114.8, 112.2, 100.7, 66.9, 63.5, 55.5, 15.0 ppm. MS (EI): *m*/*z* (%) = 271 (100) [M^+ + H], 270 (98) [M^+]: HRMS: calcd. for $C_{17}H_{18}O_3Na$ [M^+ + Na] 293.1154, found 293.1151.

5-Butoxy-3-methoxy-5,7-dihydrodibenzo[c,e]oxepine (16cd): Reaction solvent: *n*BuOH, PTSA·H_2O (15 mol-%); reaction time: 5 min; eluent: 10% EtOAc/hexane mixture; yield 85% (0.177 g, 0.593 mmol), white solid; R_f = 0.60 (EtOAc/hexane, 1:4); m.p. 30–32 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2954, 1606, 1502, 1478, 1451, 1310, 1264, 1230, 1169 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.50–7.40 (m, 3 H), 7.38–7.25 (m, 2 H), 7.14 (d, J = 2.4 Hz, 1 H), 7.01 (dd, J = 8.4, 2.4 Hz, 1 H), 5.41 (s, 1 H), 4.48 (d, J = 11.7 Hz, 1 H), 4.41 (d, J = 11.7 Hz, 1 H), 3.87 (s, 3 H), 3.78–3.58 (m, 1 H), 3.38–3.31 (m, 1 H), 1.38 (dt, J = 7.8, 6.6 Hz, 2 H), 1.15–1.03 (m, 2 H), 0.77 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.5, 140.9, 137.6, 135.9, 130.9, 129.7, 128.8, 128.5, 127.2, 126.9, 114.7, 112.5, 101.2, 67.8, 66.9, 55.4, 31.6, 19.0, 13.8 ppm. MS (EI): *m*/*z* (%) = 299 (20) [M^+ + H], 298 (100) [M^+]: HRMS: calcd. for $C_{19}H_{21}O_3$ [M^+ – H] 297.1491, found 297.1481.

5-(Benzyloxy)-3-methoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16cf): Reaction solvent: benzyl alcohol, PTSA·H_2O (15 mol-%); reaction time: 20 min; eluent: 5% EtOAc/hexane mixture; yield 80%, colourless liquid. R_f = 0.56 (EtOAc/hexane, 1:4). IR (neat):$\tilde{\nu}_{max}$ = (film): 2861, 1608, 1481, 1453, 1314, 1268, 1233, 1171 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.64–7.24 (m, 8 H), 7.12–6.89 (m, 4 H), 5.59 (s, 1 H), 4.77 (d, J = 11.8 Hz, 1 H), 4.50 (s, 2 H), 4.41 (d, J = 11.8 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.5, 141.2, 138.0, 137.3, 136.2, 133.1, 131.1, 130.0, 128.9, 129.8, 128.6, 128.1, 127.5, 127.3, 127.2, 127.1, 114.8, 113.2, 101.3, 69.0, 67.1, 55.5 ppm. HRMS: calcd. for $C_{22}H_{20}O_3Na$ [M^+ + Na] 355.1310: found 355.1307.

2,3,5-Trimethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16da): Reaction solvent: MeOH, PTSA·H_2O (15 mol-%); reaction time: 10 min; eluent: 20% EtOAc/hexane mixture; yield 90%; colourless viscous liquid. R_f = 0.50 (EtOAc/hexane, 2:3). IR (neat, film): $\tilde{\nu}_{max}$ = 2935, 1601, 1514, 1452, 1346, 1277, 1214 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.55–7.44 (m, 2 H), 7.41–7.33 (m, 2 H), 7.11 (s, 1 H), 7.03 (s, 1 H), 5.31 (s, 1 H), 4.49 (d, J = 11.6 Hz, 1 H), 4.41 (d, J = 11.6 Hz, 1 H), 3.96 (br. s, 6 H), 3.36 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 149.3, 148.7, 140.8, 136.2, 130.8, 128.9, 128.7, 128.6, 127.4, 126.9, 111.4, 110.2, 102.2, 66.7, 56.1, 56.06, 55.7 ppm. MS (EI): *m*/*z* (%) = 287 (100) [M^+ + H], 279 (70), 273 (30), 272 (60). HRMS: calcd. for $C_{17}H_{18}O_4$ [M^+ + H] 287.1283, found 287.1285.

5-Ethoxy-2,3-dimethoxy-5,7-dihydrodibenzo[c,e]oxepine (16db): Reaction solvent: EtOH, PTSA·H_2O (15 mol-%); reaction time: 10 min; eluent: 20% EtOAc/hexane mixture; yield 72%; white solid; R_f = 0.64 (EtOAc/hexane, 2:3); m.p. 100–103 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2969, 1607, 1516, 1445, 1348, 1279, 1261, 1218 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.54–7.43 (m, 2 H), 7.40–7.31 (m, 2 H), 7.16 (s, 1 H), 7.02 (s, 1 H), 5.39 (s, 1 H), 4.49 (d, J = 11.6 Hz, 1 H), 4.39 (d, J = 11.6 Hz, 1 H) 3.97 (s, 3 H), 3.96 (s, 3 H), 3.80 (dq, J = 9.4, 7.1 Hz, 1 H), 3.45 (dq, J = 9.4, 7.0 Hz, 1 H), 1.07 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 149.2, 148.7, 140.8, 136.1, 130.9, 128.9, 128.8, 128.6, 127.4, 126.9, 111.3, 110.0, 100.3, 66.7, 63.5, 56.1, 56.0, 15.0 ppm. MS (EI): *m*/*z* (%) = 323 (75) [M^+ + Na], 302 (25), 301 (100) [M^+ + H], 295 (15). HRMS: calcd. for $C_{18}H_{20}O_4$ [M^+ + H] 301.1440, found 301.1440.

5-Butoxy-2,3-dimethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16dd): Reaction solvent: *n*BuOH, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 20% EtOAc/hexane mixture; yield 84%; colourless liquid. R_f = 0.51 (EtOAc/hexane, 3:7). IR (neat, film): $\tilde{\nu}_{max}$ = 2956, 1606, 1514, 1454, 1344, 1277, 1213 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.54–7.42 (m, 2 H), 7.40–7.30 (m, 2 H), 7.13 (s, 1 H), 7.03 (s, 1 H), 5.40 (s, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 4.40 (d, J = 11.6 Hz, 1 H), 3.96 (s, 6 H), 3.75 (dt, J = 9.3, 6.7 Hz, 1 H), 3.36 (dt, J = 9.3, 6.3 Hz, 1 H), 1.46–1.37 (m, 2 H), 1.11 (dq, J = 8.4, 7.3 Hz, 2 H), 0.79 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 149.2, 148.7, 140.9, 136.3, 130.9, 129.0, 128.8, 128.7, 127.3, 126.9, 111.4, 110.2, 100.9, 67.8, 66.7, 56.1, 56.0, 31.6, 19.1, 13.8 ppm. MS (EI): *m*/*z* (%) = 351 (12) [M^+ + Na], 329 (30) [M^+ + H], 255 (92), 227 (100). HRMS: calcd. for $C_{20}H_{24}O_4$ [M^+ + H] 329.1752, found 329.1750.

2,3-Dimethoxy-5-(prop-2-ynyloxy)-5,7-dihydrodibenzo[*c*,*e*]oxepine (16de): Reaction solvent: propargyl alcohol, PTSA·H_2O (15 mol-%); reaction time: 2 h; eluent: 20% EtOAc/hexane mixture; yield 83%; colourless liquid. R_f = 0.63 (EtOAc/hexane, 2:3). IR (neat, film): $\tilde{\nu}_{max}$ = 3282, 2935, 1598, 1513, 1488, 1452, 1397, 1345, 1278, 1233, 1213 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.54 (d, J = 7.5 Hz, 1 H), 7.50–7.42 (m, 1 H), 7.39–7.30 (m, 2 H), 7.07 (s, 1 H), 7.04 (s, 1 H) 5.72 (s, 1 H), 4.47 (s, 2 H), 4.27 (dd, J = 15.9, 2.2 Hz, 1 H), 4.09 (dd, J = 15.9, 2.3 Hz, 1 H), 3.97 (s, 6 H), 2.34 (t, J = 2.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 149.4, 148.6, 140.8, 136.2, 131.2, 128.9, 128.5, 128.1, 127.3, 127.0, 111.8, 111.1, 99.7, 79.4, 74.3, 73.8, 66.8, 56.1 (2 C) ppm. MS (EI): *m*/*z* (%) = 333 (15) [M^+ + Na], 311 (5) [M^+ + H], 295 (10), 255 (100), 227 (10) (95) 212. HRMS: calcd. for $C_{19}H_{18}O_4$ [M^+ + H] 311.1283, found 311.1278.

5-(Allyloxy)-2,3-dimethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16dg): Reaction solvent: allyl alcohol, PTSA·H_2O (15 mol-%); reaction time: 2 h; eluent: 20% EtOAc/hexane mixture; yield 61%; colourless liquid. R_f = 0.66 (EtOAc/hexane, 2:3). ^1H NMR (300 MHz; $CDCl_3$): δ = 7.53 (d, J = 6.8 Hz, 1 H), 7.49–7.42 (m, 1 H), 7.39–7.30 (m, 2 H), 7.13 (s, 1 H), 7.03 (s, 1 H), 5.75 (ddd, J = 16.4, 10.6, 5.4 Hz, 1 H), 5.46 (s, 1 H), 5.07–5.00 (m, 2 H), 4.49 (d, J = 11.6 Hz, 1 H), 4.42 (d, J = 11.6 Hz, 1 H), 4.25–4.20 (m, 1 H), 4.00 (s, 1 H), 3.96 (s, 6 H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 149.3, 148.7, 140.9, 136.2, 134.3, 131.0, 128.9, 128.7, 128.6, 127.4, 126.9, 116.4, 111.4, 110.3, 100.2, 68.4, 66.8, 56.1, 56.08 ppm. MS (EI): *m*/*z* (%) = 335 (4) [M^+ + Na], 313 (5) [M^+ + H], 255 (100), 227 (98), 225 (15), 212 (12). HRMS: calcd. for $C_{19}H_{20}O_4$ [M^+ + H] 313.1440, found 313.1445.

2,3,9-Trimethoxy-5-propoxy-5,7-dihydrodibenzo[*c*,*e*]oxepine (16ec): Reaction solvent: *n*PrOH, PTSA·H_2O (15 mol-%); reaction time: 20 min; eluent: 10% EtOAc/hexane mixture; yield 76%; transparent crystals. R_f = 0.47 (EtOAc/hexane, 2:3); m.p. 65–70 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 1609, 1497, 1459, 1256 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.45 (d, J = 8.3 Hz, 1 H), 7.14 (s, 1 H), 7.01–6.95 (m, 3 H), 5.37 (s, 1 H), 4.47 (d, J = 11.6 Hz, 1 H), 4.37 (d, J = 11.6 Hz, 1 H), 3.95 (s, 6 H), 3.87 (s, 3 H), 3.73 (dt, J = 9.1, 6.7 Hz, 1 H), 3.35 (dt, J = 9.1, 6.5 Hz, 1 H), 1.50 (dq, J = 9.0, 6.9 Hz, 2 H), 0.75 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.0, 149.2, 148.3, 137.5, 133.3, 130.8, 128.5, 128.0, 114.2, 114.1, 111.1, 110.2, 100.8, 69.9, 66.8, 56.1, 56.0, 55.4, 22.9, 10.5 ppm. MS (EI): *m*/*z* (%) = 367 (12) [M^+ + Na], 345 (15) [M^+ + H], 325 (10), 285 (100), 257 (45). HRMS: calcd. for $C_{20}H_{24}O_5$ [M^+ + H] 345.1702, found 345.1700.

2,3-Dimethoxy-5-propoxy-5,7-dihydro-6,9,11-trioxabenzo[3,4]-cyclohepta[1,2-*f*]indene (16fc): Reaction solvent: *n*PrOH, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 5% EtOAc/hexane mixture; yield 85%; white solid; R_f = 0.50 (EtOAc/hexane, 3:7); m.p. 88–90 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2860, 1607, 1428, 1267, 1238 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.14 (s, 1 H), 7.00 (s, 1 H), 6.93 (s, 1 H), 6.88 (s, 1 H), 6.01 (2 s overlapping, 2 H), 5.35 (s, 1 H), 4.37 (d, J = 11.7 Hz, 1 H), 4.26 (d, J = 11.7 Hz, 1 H), 3.95 (s, 6 H), 3.73 (dt, J = 9.2, 6.7 Hz, 1 H), 3.36 (dt, J = 9.2, 6.5 Hz, 1 H), 1.60–1.45 (m, 2 H), 0.78 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 149.2, 148.5, 148.0, 146.7, 134.9, 130.9, 130.0, 128.8, 110.9, 109.9, 109.2, 107.5, 101.3, 100.6, 70.0, 66.4, 56.1, 56.0, 22.9, 10.5 ppm. MS (EI): *m*/*z* (%) = 359 (100) [M^+ + H], 357 (20). HRMS: calcd. for $C_{20}H_{22}O_6$ [M^+ + H] 359.1495, found 359.1498.

7-Methoxy-5,7-dihydro-6,9,11-trioxabenzo[3,4]cyclohepta[1,2-*f*]indene (16ga): Reaction solvent: MeOH, PTSA·H_2O (15 mol-%); reaction time: 10 min; eluent: 20% EtOAc/hexane mixture; yield 72%; white solid; R_f = 0.57 (EtOAc/hexane, 3:7); m.p. 147–150 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2915, 1485, 1448, 1370, 1267, 1228, 1201 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.48–7.42 (m, 2 H), 7.40–7.30 (m, 2 H), 7.06 (s, 1 H), 6.99 (s, 1 H), 6.03 (2 s, overlapping, 2 H), 5.23 (s, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 4.40 (d, J = 11.6 Hz, 1 H), 3.32 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 148.1, 147.4, 140.7, 135.9, 132.6, 130.1, 128.9, 128.6, 127.5, 127.0, 108.5, 107.6, 102.0, 101.4, 66.7, 55.7 ppm. MS (EI): *m*/*z* (%) = 271 (100) [M^+ + H], 269 (2). HRMS: calcd. for $C_{16}H_{14}O_4$ [M^+ + H] 271.0970, found 271.0977.

7-Propoxy-5,7-dihydro-6,9,11-trioxabenzo[3,4]cyclohepta[1,2-*f*]indene (16gc): Reaction solvent: *n*PrOH, PTSA·H_2O (15 mol-%); reaction time: 20 min; eluent: 10% EtOAc/hexane mixture; yield 89%; white solid; R_f = 0.70 (EtOAc/hexane, 3:7); m.p. 65–68 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2965, 1503, 1478, 1452, 1420, 1375, 1346, 1265, 1188 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.47–7.41 (m, 2 H), 7.39–7.29 (m, 2 H), 7.11 (s, 1 H), 6.99 (s, 1 H), 6.03 (2 s, overlapping, 2 H), 5.30 (s, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 4.38 (d, J = 11.6 Hz, 1 H), 3.67 (dt, J = 9.2, 6.8 Hz, 1 H), 3.29 (dt, J = 9.2, 6.4 Hz, 1 H), 1.51–1.37 (m, 2 H), 0.69 (t, J = 7.4 Hz, 3 H) ppm.

^{13}C NMR (75 MHz; $CDCl_3$): δ = 148.0, 147.4, 140.8, 135.9, 132.6, 130.5, 128.8, 128.6, 127.5, 127.0, 108.4, 107.5, 101.4, 100.5, 69.9, 66.7, 22.8, 10.4 ppm. MS (EI): *m*/*z* (%) = 299 (20) [M^+ + H], 279 (30), 239 (100), 211 (40). HRMS: calcd. for $C_{18}H_{18}O_4$ [M^+ + H] 299.1283, found 299.1293.

7-(2-Propynyloxy)-5,7-dihydro-6,9,11-trioxabenzo[3,4]cyclohepta-[1,2-*f*]indene (16ge): Reaction solvent: propargyl alcohol, PTSA·H_2O (15 mol-%); reaction time: 1 h, eluent: 10% EtOAc/hexane mixture; yield 81%; white solid; R_f = 0.54 (EtOAc/hexane, 3:7); m.p. 65–68 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3274, 2869, 1501, 1477, 1450, 1417, 1365, 1344, 1266 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.50–7.41 (m, 2 H), 7.35–7.26 (m, 2 H), 7.02 (s, 1 H), 7.01 (s, 1 H), 6.04 (s, 1 H), 6.03 (s, 1 H), 5.63 (s, 1 H), 4.46 (s, 2 H), 4.22 (dd, *J* = 15.9, 2.2 Hz, 1 H), 4.05 (dd, *J* = 15.9, 2.3 Hz, 1 H), 2.32 (t, *J* = 2.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 148.3, 147.3, 140.8, 135.9, 132.9, 129.4, 129.0, 128.5, 127.5, 127.1, 108.8, 108.3, 101.5, 99.5, 79.2, 74.3, 66.8, 54.1 ppm. MS (EI): *m*/*z* (%) = 299 (8) [M^+ + Na], 239 (100), 227 (97), 177 (42). HRMS: calcd. for $C_{18}H_{14}O_4$ [M^+ + Na] 317.0790, found 317.0786; calcd. for $C_{15}H_{11}O_3^+$ [M – OCH_2CCH]$^+$ 239.0708, found 239.0712.

3,7-Dimethoxy-5,7-dihydro-6,9,11-trioxabenzo[3,4]cyclohepta[1,2-*f*]-indene (16ha): Reaction solvent: MeOH, PTSA·H_2O (15 mol-%); reaction time: 20 min; eluent: 20% EtOAc/hexane mixture; yield 96%; white solid; R_f = 0.50 (EtOAc/hexane, 3:7); m.p. 121–123 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2803, 1608, 1475, 1239, 1163 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.38 (d, *J* = 8.4 Hz, 1 H), 7.05 (s, 1 H), 6.98 (dd, *J* = 8.4, 2.7 Hz, 1 H), 6.93 (s, 2 H), 6.02 (d, *J* = 1.4 Hz, 1 H), 6.01 (d, *J* = 1.4 Hz, 1 H), 5.21 (s, 1 H), 4.45 (d, *J* = 11.6 Hz, 1 H), 4.36 (d, *J* = 11.6 Hz, 1 H), 3.86 (s, 3 H), 3.34 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.1, 148.1, 146.9, 137.2, 133.2, 132.4, 129.6, 128.2, 114.2, 114.1, 108.2, 107.5, 102.0, 101.3, 66.8, 55.7, 55.4 ppm. MS (EI): *m*/*z* (%) = 323 (8) [M^+ + Na], 301 (2) [M^+ + H], 269 (100), 241 (60), 211 (20). HRMS: calcd. for $C_{17}H_{16}O_5$ [M^+ + H] 301.1076, found 301.1086.

7-Ethoxy-3-methoxy-5,7-dihydro-6,9,11-trioxabenzo[3,4]cyclohepta-[1,2-*f*]indene (16hb): Reaction solvent: EtOH, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 10% EtOAc/hexane mixture; yield 84%; white solid; R_f = 0.61 (EtOAc/hexane, 3:7); m.p. 127–129 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2874, 1610, 1474, 1429, 1376, 1305, 1263, 1241, 1188 cm^{-1}. ^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.38 (d, *J* = 8.4 Hz, 1 H), 7.12 (s, 1 H), 6.98 (dd, *J* = 8.4, 2.7 Hz, 1 H), 6.94–6.93 (m, 2 H), 6.02 (d, *J* = 1.4 Hz, 1 H), 6.01 (d, *J* = 1.4 Hz, 1 H), 5.27 (s, 1 H), 4.45 (d, *J* = 11.6 Hz, 1 H), 4.34 (d, *J* = 11.6 Hz, 1 H), 3.86 (s, 3 H), 3.79 (dq, *J* = 9.4, 7.1 Hz, 1 H), 3.43 (dq, *J* = 9.4, 7.0 Hz, 1 H), 1.09 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 159.1, 148.0, 147.0, 137.1, 133.2, 132.4, 129.9, 128.2, 114.2 (2 C), 108.1, 107.2, 101.3, 100.0, 66.8, 63.8, 55.4, 15.1 ppm. MS (EI): *m*/*z* (%) = 337 (8) [M^+ + Na], 315 (15) [M^+ + H], 269 (100), 241 (60), 211 (20). HRMS: calcd. for $C_{18}H_{18}O_5$ [M^+ + H] 315.1214, found 315.1238.

3-Methoxy-7-propoxy-5,7-dihydro-6,9,11-trioxabenzo[3,4]cyclo-hepta[1,2-*f*]indene (16hc): Reaction solvent: *n*PrOH, PTSA·H_2O (15 mol-%); reaction time: 60 min; eluent: 10% EtOAc/hexane mixture; yield 84%; white solid; R_f = 0.60 (EtOAc/hexane, 3:7); m.p. 94–98 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2969, 1474, 1432, 1378, 1310, 1266, 1186 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.38 (d, *J* = 8.4 Hz, 1 H), 7.11 (s, 1 H), 7.00–6.93 (m, 3 H), 6.02 (d, *J* = 1.3 Hz, 1 H), 6.01 (d, *J* = 1.3 Hz, 1 H), 5.27 (s, 1 H), 4. 45 (d, *J* = 11.5 Hz, 1 H), 4.35 (d, *J* = 11.5 Hz, 1 H), 3.86 (s, 3 H), 3.70 (dt, *J* = 9.2, 6.7 Hz, 1 H), 3.31 (dt, *J* = 9.2, 6.4 Hz, 1 H), 1.54–1.43 (m, 2 H), 0.74 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.1, 148.0, 146.9, 137.2, 133.2, 132.4, 129.9, 128.2, 114.2 (2 C), 108.1, 107.3, 101.3, 100.4, 70.0, 66.8, 55.4, 22.8, 10.5 ppm. MS (EI): *m*/*z* (%) = 329 (20) [M^+ + H], 269 (100), 241 (60), 211 (20). HRMS: calcd. for $C_{19}H_{21}O_5$ [M^+ + H] 329.1389, found 329.1405.

7-Butoxy-3-methoxy-5,7-dihydro-6,9,11-trioxabenzo[3,4]cyclohepta-[1,2-*f*]indene (16hd): Reaction solvent: MeOH, PTSA·H_2O (15 mol-%); reaction time: 20 min; eluent: 20% EtOAc/hexane mixture; yield 97%; white solid; R_f = 0.66 (EtOAc/hexane, 3:7); m.p. 68–70 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2955, 1474, 1376, 1263, 1240, 1182 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.38 (d, *J* = 8.3 Hz, 1 H), 7.09 (s, 1 H), 7.00–6.93 (m, 3 H), 6.02 (s, 1 H), 6.01 (s, 1 H), 5.27 (s, 1 H), 4.36 (d, *J* = 11.7 Hz, 1 H), 4.24 (d, *J* = 11.7 Hz, 1 H), 3.86 (s, 3 H), 3.75 (dt, *J* = 9.3, 6.6 Hz, 1 H), 3.34 (dt, *J* = 9.3, 6.3 Hz, 1 H), 1.49–140 (m, 2 H), 1.20–1.10 (m, 2 H), 0.81 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.1, 148.0, 146.9, 137.2, 133.2, 132.4, 129.9, 128.2, 114.2, 114.1, 108.1, 107.4, 101.3, 100.5, 68.1, 66.8, 55.4, 31.7, 19.1, 13.8 ppm. MS (EI): *m*/*z* (%) = 365 (2) [M^+ + Na], 343 (20) [M^+ + H], 269 (100), 241 (60), 211 (18). HRMS: calcd. for $C_{20}H_{22}O_5$ [M^+ + H] 343.1545, found 343.1557.

5-Methoxy-5,7-dihydro-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*c*][1,3]diox-olo[4′,5′:4,5]benzo[1,2-*e*]oxepine (16ia): Reaction solvent: MeOH, PTSA·H_2O (15 mol-%); reaction time: 60 min; eluent: 20% EtOAc/hexane mixture; yield 89%; white solid; R_f = 0.54 (EtOAc/hexane, 3:7); m.p. 185–188 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2894, 1475, 1429, 1390, 1357, 1244, 1210 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.04 (s, 1 H), 6.93 (s, 1 H), 6.90 (s, 1 H), 6.87 (s, 1 H), 6.02 (s, 4 H), 5.19 (s, 1 H), 4.36 (d, *J* = 11.7 Hz, 1 H), 4.26 (d, *J* = 11.7 Hz, 1 H), 3.35 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 148.1, 147.1, 146.9, 134.7, 132.5, 129.9, 129.7, 109.4, 109.0, 108.2, 107.5, 107.4, 102.0, 101.4, 101.3, 66.4, 55.8 ppm. MS (EI): *m*/*z* (%) = 337 (5) [M^+ + Na], 283 (25), 255 (100), 225 (12). HRMS: calcd. for $C_{17}H_{14}O_6$ [M^+ + Na] 337.0697, found 337.0695.

5-Propoxy-5,7-dihydro-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*c*][1,3]diox-olo[4′,5′:4,5]benzo[1,2-*e*]oxepine (16ic): Reaction solvent: *n*PrOH, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 10% EtOAc/hexane mixture; yield 63%; white solid; R_f = 0.67 (EtOAc/hexane, 3:7); m.p. 174–176 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2866, 1502, 1477, 1432, 1356, 1241, 1182 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.11 (s, 1 H), 6.93 (s, 1 H), 6.90 (s, 1 H), 6.87 (s, 1 H), 6.03–6.00 (m, 4 H), 5.25 (s, 1 H), 4. 37 (d, *J* = 11.7 Hz, 1 H), 4.24 (d, *J* = 11.7 Hz, 1 H), 3.70 (dt, *J* = 9.2, 6.7 Hz, 1 H), 3.32 (dt, *J* = 9.2, 6.5 Hz, 1 H), 1.50 (dt, *J* = 14.0, 7.0 Hz, 2 H), 0.78 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 148.04, 148.02, 147.2, 146.8, 134.8, 132.5, 130.2, 129.7, 109.1, 108.0, 107.6, 107.2, 101.4, 101.3, 100.3, 70.1, 66.3, 22.9, 10.5 ppm. MS (EI): *m*/*z* (%) = 365 (4) [M^+ + Na], 283 (30), 255 (100), 225 (12). HRMS: calcd. for $C_{19}H_{18}O_6$ [M^+ + Na] 365.1000, found 365.0998.

7-Butoxy-3-methoxy-5,7-dihydro-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*c*]-benzo[*e*]oxepine (16id): Reaction solvent: *n*BuOH, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 10% EtOAc/hexane mixture; yield 78%; white solid; R_f = 0.62 (EtOAc/hexane, 3:7); m.p. 146–148 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2875, 1504, 1478, 1434, 1356, 1243, 1183 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$): δ = 7.09 (s, 1 H), 6.93 (s, 1 H), 6.89 (s, 1 H), 6.86 (s, 1 H), 6.02–6.00 (m, 4 H), 5.25 (s, 1 H), 4.37 (d, *J* = 11.6 Hz, 1 H), 4.24 (d, *J* = 11.6 Hz, 1 H), 3.75 (dt, *J* = 9.2, 6.6 Hz, 1 H), 3.35 (dt, *J* = 9.2, 6.3 Hz, 1 H), 1.51–1.41 (m, 2 H), 1.28–1.13 (m, 2 H), 0.83 (t, *J* = 7.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 148.04, 148.02, 147.1, 146.8, 134.8, 132.5, 130.2, 129.7, 109.1, 108.0, 107.6, 107.3, 101.4, 101.3, 100.4, 68.1, 66.3, 31.7, 19.1, 13.8 ppm. MS (EI): *m*/*z* (%) = 379 (2) [M^+ + Na], 283 (32), 255 (100), 225 (12). HRMS: calcd. for $C_{20}H_{20}O_6$ [M^+ + Na] 379.1158, found 379.1166.

General Procedure for the Preparation of 5-(Phenylthio)-5,7-dihydrodibenzo[*c*,*e*]oxepines 17 and {2′-[Bis(phenylsulfanyl)methyl]-1,1′-biphenyl-2-yl}methanols 18: *p*-Toluenesulfonic acid monohydrate (15 mol-%) was added to a solution of the substituted benzyl alcohol **15** (0.7 mmol) in benzenethiol (5 mL), at room temp. The reaction mixture was then stirred at this temperature for 10–30 min until the reaction was deemed complete (TLC). The solution was then concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with Na_2CO_3 solution (20 mL, 10%), followed by brine (20 mL), after which they were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography using suitable solvent mixture of EtOAc/hexane as eluent to afford the desired 5-(phenylthio)-5,7-dihydrodibenzo[*c*,*e*]oxepines as described below. It should be noted that in three examples, the dithiophenyl compounds **18** were isolated instead. For these three compounds HRMS proved to be difficult to achieve as under most conditions, the corresponding ring-closed O,S-thioacetal was obtained instead. Compounds **18** were investigated by electrospray mass spectrometry (ESMS) and atmospheric pressure chemical ionization (APCI). In addition, an atmospheric solids analysis probe (ASAP) was also utilized, which is a solids technique that uses APCI to ionize molecules from the tip of a melting point tube (without the use of solvent).

5-(Phenylsulfanyl)-5,7-dihydrodibenzo[*c*,*e*]oxepine (17ai): Reaction solvent: thiophenol, PTSA·H_2O (15 mol-%); reaction time: 10 min; eluent: 5% EtOAc/hexane mixture; yield 70%; white solid; R_f = 0.54 (EtOAc/hexane, 1:4); m.p. 86–88 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2866, 1579, 1477, 1438, 1375, 1205 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.63–7.49 (m, 4 H), 7.46–7.44 (m, 2 H), 7.40–7.32 (m, 4 H), 7.24–7.16 (m, 3 H), 6.22 (s, 1 H), 4.62 (d, J = 11.7 Hz, 1 H), 4.55 (d, J = 11.7 Hz, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 140.8, 139.5, 136.9, 136.5, 135.7, 131.3 (2 C), 129.4 (2 C), 129.2, 129.0, 128.7 (3 C), 128.3, 128.2, 127.8, 126.8, 90.2, 68.0 ppm. MS (EI): *m*/*z* (%) = 327 (100) [M^+ + Na], 229 (70), 217 (35), 195 (60). HRMS: calcd. for $C_{20}H_{16}OS$ [M^+ + Na] 327.0820, found 327.0834.

3-Methoxy-7-(phenylsulfanyl)-5,7-dihydrodibenzo[*c*,*e*]oxepine (17bi): Reaction solvent: thiophenol, PTSA·H_2O (15 mol-%); reaction time: 30 min; eluent: 5% EtOAc/hexane mixture; yield 86%; white solid; R_f = 0.50 (EtOAc/hexane, 1:4); m.p. 100–102 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2864, 1611, 1580, 1505, 1479, 1449, 1376, 1261, 1230 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.54–7.44 (m, 3 H), 7.36–7.33 (m, 4 H), 7.25–7.16 (m, 3 H), 7.07 (dd, J = 8.4, 2.6 Hz, 1 H), 7.00 (d, J = 2.6 Hz, 1 H), 6.22 (s, 1 H), 4.57 (d, J = 11.7 Hz, 1 H), 4.52 (d, J = 11.7 Hz, 1 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 160.1, 139.4, 137.1, 136.2, 133.2, 131.2 (2 C), 129.4, 128.9 (2 C), 128.7 (3 C), 128.3, 127.7, 126.8, 114.8, 114.6, 90.4, 68.2, 55.4 ppm. MS (EI): *m*/*z* (%) = 373 (100), 357 (40) [M^+ + Na], 335 (25) [M^+ + H], 317 (15). HRMS: calcd. for $C_{21}H_{18}O_2S$ [M^+ + H] 335.1106, found 335.1109.

3-Methoxy-5-(phenylsulfanyl)-5,7-dihydrodibenzo[*c*,*e*]oxepine (17ci): Reaction solvent: thiophenol, PTSA·H_2O (15 mol-%); reaction time: 15 min; eluent: 20% EtOAc/hexane mixture; yield 90%; white solid; R_f = 0.63 (EtOAc/hexane, 3:7); m.p. 87–90 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 2861, 1608, 1580, 1478, 1438, 1376, 1287, 1253 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.57–7.48 (m, 3 H), 7.43–7.34 (m, 4 H), 7.23–7.13 (m, 3 H), 7.03 (dd, J = 8.5, 2.4 Hz, 1 H), 6.93 (d, J = 2.3 Hz, 1 H), 6.17 (s, 1 H), 4.61, (d, J = 11.7 Hz, 1 H), 4.54 (d, J = 11.7 Hz, 1 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.5, 140.7, 137.7, 136.9, 135.5, 131.9, 131.3 (2 C), 130.3, 129.4, 129.2, 128.7 (2 C), 128.1, 127.5, 126.9, 115.0, 113.6, 90.3, 68.2, 55.5 ppm. MS (EI): *m*/*z* (%) = 335 (15) [M^+ + H], 334 (100) [M^+]: HRMS: calcd. for $C_{21}H_{18}O_2S$ [M^+] 334.1027, found 334. 1028.

[2-(6-{Bis(phenylsulfanyl)methyl}-1,3-benzodioxol-5-yl)-5-methoxyphenyl]methanol (18hi): Reaction solvent: thiophenol, PTSA·H_2O (15 mol-%); reaction time: 2 h, eluent: 20% EtOAc/hexane mixture; yield 87%, white viscous material; R_f = 0.37 (EtOAc/hexane, 2:3). IR (neat):$\tilde{\nu}_{max}$ = (film): 3047, 2893, 1605, 1570, 1496, 1472, 1353, 1234, 1218, 1153, 1118 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.41 (s, 1 H), 7.31–7.15 (m, 9 H), 7.10 (d, J = 2.6 Hz, 1 H), 6.69 (dd, J = 8.4, 2.7 Hz, 1 H), 6.57–6.44 (m, 2 H), 6.05 (s, 2 H), 5.13 (s, 1 H), 4.29–4.04 (m, 2 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.5, 147.5, 146.9, 141.2, 134.0, 133.7, 133.2, 132.2, 131.3, 131.0, 129.8, 128.9, 128.8, 128.2, 112.9, 112.8, 109.7, 108.5, 101.4, 62.6, 58.5, 55.4 ppm. HRMS: no corresponding ions could be identified in the mass spectrum of this compound; only the cyclized **17hi** was detected (calcd. for $C_{22}H_{19}O_4S$ [M^+ + H], found 379.1012), indicating cyclization under ionization. Please see text in main body of paper and explanation above in general description of the synthesis of compounds **17** and **18**.

{6′-[Bis(phenylsulfanyl)methyl]-2′,3′,4′-trimethoxy-1,1′-biphenyl-2-yl}methanol (18ji): Reaction solvent: thiophenol, PTSA·H_2O (10 mol-%); reaction time: 12 h, eluent: 20% EtOAc/hexane mixture; yield 90%, colourless liquid; R_f = 0.40 (EtOAc/hexane, 2:3). IR (neat): $\tilde{\nu}_{max}$ = (film) 2933, 2833, 1593, 1478, 1454, 1397, 1326, 1272, 1142 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.54 (d, J = 6.8 Hz, 1 H), 7.48–7.37 (m, 1 H), 7.33–7.11 (m, 10 H), 7.05–6.98 (m, 2 H), 6.87 (d, J = 6.8 Hz, 1 H), 5.09 (s, 1 H), 4.05–3.99 (m, 2 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 3.49 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 153.1, 150.1, 141.8, 140.5, 134.0, 133.7, 133.6, 133.3, 133.3 (2 C), 130.2 (4 C), 129.7, 128.9, 128.9, 128.5, 128.2, 128.2, 127.4 (2 C), 126.1, 108.0, 63.5, 61.2, 61.1, 58.3, 56.1 ppm. HRMS: calcd. for $C_{30}H_{30}O_5S_2Na$ [M^+ + Na] 557.1432, found 557.1415; calcd. for $C_{30}H_{34}NO_5S_2$ [M^+ + NH_4] 552.1878, found 552.1875.

{6′-[Bis(phenylsulfanyl)methyl]-2′,3′,4,4′-tetramethoxy-1,1′-biphenyl-2-yl}methanol (18ki): Reaction solvent: thiophenol, PTSA·H_2O (15 mol-%); reaction time: 12 h, eluent: 20% EtOAc/hexane mixture; yield 71%; colourless liquid; R_f = 0.54 (EtOAc/hexane, 2:3). IR (neat): $\tilde{\nu}_{max}$ = (film) 3054, 2932, 1593, 1476, 1431, 1398, 1324, 1142 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.34–7.13 (m, 9 H), 7.10–7.01 (m, 3 H), 6.80 (s, 2 H), 5.15 (s, 1 H), 3.98 (br. s, 1 H), 3.96 (br. s, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.48 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.6, 153.0, 150.4, 141.8, 141.8, 134.0, 133.7, 133.6, 133.3, 133.2, 131.3, 128.9 (2 C), 128.8 (2 C), 128.2, 128.1, 125.8, 125.7, 114.2, 113.5, 108.0, 63.6, 61.2, 61.1, 58.1, 56.1, 55.3 ppm. HRMS: calcd. for $C_{29}H_{28}O_4S_2Na$ [M^+ + Na] 527.1327, found 527.1310; calcd. for $C_{29}H_{32}NO_4S_2$ [M^+ + NH_4] 522.1773, found 522.1769.

General Procedure for the Preparation of 5-Phenoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines 19: *p*-Toluenesulfonic acid monohydrate (15–25 mol-%) was added to a solution of the substituted benzyl alcohol **15** (0.7 mmol) in phenol (5 mL) at room temp. The reaction mixture was then stirred at this temperature for 5–48 h until the reaction was deemed complete (TLC). The solution was then concentrated under reduced pressure, diluted with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with Na_2CO_3 solution (20 mL, 10%), followed by brine (20 mL), after which they were dried (Na_2SO_4) and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography using suitable solvent

mixture of EtOAc/hexane as eluent to afford the desired 5-phenoxy-5,7-dihydrodibenzo[*c*,*e*]oxepines **19** as described below.

4-(5,7-Dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenol (19aj): Reaction solvent: phenol, PTSA·H_2O (15 mol-%); reaction time: 5 h; eluent: 20% EtOAc/hexane mixture; yield 73%; white solid; R_f = 0.37 (EtOAc/hexane, 3:7); m.p. 160–164 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3248, 1601, 1511, 1448, 1368, 1236 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.60–7.49 (m, 3 H), 7.47–7.40 (m, 3 H), 7.30–7.20 (m, 3 H), 6.82 (d, J = 7.6 Hz, 1 H), 6.79 (s, 1 H), 6.77 (s, 1 H), 5.35 (s, 1 H), 5.13 (s, 1 H), 4.69 (d, J = 11.4 Hz, 1 H), 4.35 (d, J = 11.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 155.1, 141.2, 140.8, 138.2, 134.9, 131.9, 129.4, 129.1, 128.9 (2 C), 128.7, 128.4 (2 C), 128.1, 127.7, 127.5, 115.1 (2 C), 76.6, 68.0 ppm. MS (EI): *m*/*z* (%) = 290 (15) [M^+], 289 (100) [M^+ + H]. HRMS: calcd. for $C_{20}H_{16}O_2$ [M^+ + H] 289.1229, found 289.1222.

4-(9-Methoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenol (19bj): Reaction solvent: phenol, PTSA·H_2O (20 mol-%); reaction time: 8 h; eluent: 20% EtOAc/hexane mixture; yield 81%; light yellow solid; R_f = 0.43 (EtOAc/hexane, 3:7); m.p. 65–70 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3311, 1610, 1579, 1504, 1478, 1440, 1424, 1376, 1304, 1289, 1260, 1229, 1187 cm^{-1}. ^1H NMR (500 MHz; $CDCl_3$): δ = 7.52–7.45 (m, 2 H), 7.41–7.37 (m, 1 H), 7.24 (d, J = 8.2 Hz, 1 H), 7.21 (s, 1 H), 7.20 (s, 1 H), 7.05 (dd, J = 8.4, 2.6 Hz, 1 H), 6.99 (d, J = 2.6 Hz, 1 H), 6.84 (d, J = 7.8 Hz, 1 H), 6.78 (s, 2 H), 6.76 (s, 1 H), 5.43 (br. s, 1 H), 5.35 (s, 1 H), 4.63 (d, J = 11.4 Hz, 1 H), 4.34 (d, J = 11.4 Hz, 1 H), 3.87 (s, 3 H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 159.7, 155.1, 140.7, 138.0, 136.3, 133.7, 132.1, 128.9 (2 C), 128.8, 128.7, 128.4, 127.5, 127.4, 115.1 (2 C), 114.7, 114.5, 76.8, 68.2, 55.5 ppm. MS (EI): *m*/*z* (%) = 319 (25) [M^+ + H], 289 (100), 225 (18), 195 (72). HRMS: calcd. for $C_{21}H_{18}O_3$ [M^+ + H] 319.1334, found 319.1332.

4-(3-Methoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenol (19cj): Reaction solvent: phenol, PTSA·H_2O (15 mol-%); reaction time: 5 h; eluent: 20% EtOAc/hexane mixture; (0.177 g, 0.588 mmol), yield 80%; light yellow solid; R_f = 0.36 (EtOAc/hexane, 3:7); m.p. 67–70 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 1607, 1514, 1478, 1450, 1368, 1277, 1217 cm^{-1}. ^1H NMR (500 MHz; $CDCl_3$): δ = 7.58 (d, J = 7.0 Hz, 1 H), 7.56–7.50 (m, 2 H), 7.47 (d, J = 6.3 Hz, 1 H), 7.44–7.40 (m, 1 H), 7.24 (s, 1 H), 7.23 (s, 1 H), 7.01 (dd, J = 8.4, 2.7 Hz, 1 H), 6.78 (s, 1 H), 6.76 (s, 1 H), 6.48 (d, J = 2.6 Hz, 1 H), 5.85 (br. s, 1 H), 5.38 (s, 1 H), 4.74 (d, J = 11.5 Hz, 1 H), 4.41 (d, J = 11.4 Hz, 1 H), 3.75 (s, 3 H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 159.3, 155.2, 141.0, 139.7, 134.6, 133.4, 131.5, 129.3, 129.0, 128.8 (3 C), 127.8, 127.2, 115.1 (2 C), 114.9, 113.2, 76.6, 68.1, 55.2 ppm. MS (EI): *m*/*z* (%) = 319 (12) [M^+ + H], 318 (100) [M^+]: HRMS: calcd. for $C_{21}H_{18}O_3$ [M^+ + H] 319.1334, found 319.1343.

4-(2,3-Dimethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenol (19dj): Reaction solvent: phenol, PTSA·H_2O (20 mol-%); reaction time: 12 h; eluent: 30% EtOAc/hexane mixture; yield 75%; light yellow solid; R_f = 0.36 (EtOAc/hexane, 2:3); m.p. 75–80 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3428, 1601, 1510, 1442, 1399, 1334, 1203 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.59–7.49 (m, 2 H), 7.45–7.37 (m, 2 H), 7.24 (s,1 H), 7.21 (s, 1 H), 7.05 (s, 1 H), 6.81 (s, 1 H), 6.78 (s, 1 H), 6.37 (s, 1 H), 5.48 (s, 1 H), 5.29 (s, 1 H), 4.68 (d, J = 11.3 Hz, 1 H), 4.32 (d, J = 11.3 Hz, 1 H), 3.95 (s, 3 H), 3.66 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 155.0, 148.8, 148.6, 141.3, 135.1, 133.4, 132.2, 131.1, 129.5, 128.9, 128.8 (2 C), 127.9, 127.1, 115.1 (2 C), 112.0, 110.7, 76.3, 68.0, 56.1, 55.8 ppm. MS (EI): *m*/*z* (%) = 349 (28) [M^+ + H], 320 (25), 319 (90), 255 (25), 225 (100). HRMS: calcd. for $C_{22}H_{20}O_4$ [M^+ + H] 349.1440, found 349.1443.

4-(2,3,9-Trimethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenol (19ej): Reaction solvent: phenol, PTSA·H_2O (20 mol-%); reaction time: 15 h; eluent: 30% EtOAc/hexane mixture; yield 75%; light reddish solid; R_f = 0.33 (EtOAc/hexane, 2:3); m.p. 75–80 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3427, 2939, 1610, 1495, 1448, 1401, 1337, 1308, 1252, 1204 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.49 (d, J = 8.4 Hz, 1 H), 7.22 (s, 1 H), 7.20 (s, 1 H), 7.05 (dd, J = 8.4, 2.6 Hz, 1 H), 7.01–6.96 (m, 2 H), 6.80 (s, 1 H), 6.76 (s, 1 H), 6.36 (s, 1 H), 5.87 (br. s, 1 H), 5.29 (s, 1 H), 4.63 (d, J = 11.3 Hz, 1 H), 4.31 (d, J = 11.3 Hz, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H), 3.65 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.4, 155.1, 148.8, 148.1, 136.4, 133.7, 133.4, 132.2, 130.7, 128.7 (2 C), 128.2, 115.1 (2 C), 114.6, 114.5, 112.1, 110.6, 76.6, 68.2, 56.0, 55.8, 55.5 ppm. MS (EI): *m*/*z* (%) = 379 (45) [M^+ + H], 377 (20), 349 (100). HRMS: calcd. for $C_{23}H_{22}O_5$ [M^+ + H] 379.1545, found 379.1549.

4-(5*H*,7*H*-6,9,11-Trioxabenzo[3,4]cyclohepta[1,2-*f*]inden-7-yl)phenol (19gj): Reaction solvent: phenol, PTSA·H_2O (15 mol-%); reaction time: 15 h; eluent: 20% EtOAc/hexane mixture; yield 86%; light yellow solid; R_f = 0.50 (EtOAc/hexane, 3:7); m.p. 82–85 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3303, 1612, 1503, 1476, 1449, 1364, 1213 cm^{-1}. ^1H NMR (500 MHz; $CDCl_3$): δ = 7.52–7.48 (m, 2 H), 7.42–7.37 (m, 2 H), 7.19 (s, 1 H), 7.17 (s, 1 H), 7.00 (s, 1 H), 6.77 (s, 1 H), 6.75 (s, 1 H), 6.33 (s, 1 H), 5.96–5.93 (m, 2 H), 5.73 (br. s, 1 H), 5.20 (s, 1 H), 4.67 (d, J = 11.3 Hz, 1 H), 4.31 (d, J = 11.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 155.2, 147.5, 147.3, 141.2, 134.9, 134.8, 132.5, 131.8, 129.4, 129.0, 128.8 (2 C), 128.1, 127.2, 115.1 (2 C), 109.1, 107.9, 101.3, 76.0, 67.9 ppm. MS (EI): *m*/*z* (%) = 355 (2) [M^+ + Na], 333 (45) [M^+ + H], 303 (100), 239 (28), 209 (60). HRMS: calcd. for $C_{21}H_{16}O_4$ [M^+ + H] 333.1127, found 333.1136.

4-(3-Methoxy-5*H*,7*H*-6,9,11-trioxabenzo[3,4]cyclohepta[1,2-*f*]inden-7-yl)phenol (19hj): Reaction solvent: phenol, PTSA·H_2O (20 mol-%); reaction time: 20 h; eluent: 30% EtOAc/hexane mixture; yield 85%; light yellow solid; R_f = 0.40 (EtOAc/hexane, 2:3); m.p. 85–90 °C. IR (neat, film): $\tilde{\nu}_{max}$ = 3278, 1608, 1499, 1473, 1367, 1235 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.44 (d, J = 8.4 Hz, 1 H), 7.21 (s, 1 H), 7.18 (s, 1 H), 7.04 (dd, J = 8.4, 2.4 Hz, 1 H), 6.98–6.96 (m, 2 H), 6.79 (s, 1 H), 6.76 (s, 1 H) 6.31 (s, 1 H), 5.95 (s, 2 H), 5.41 (br. s, 1 H), 5.20 (s, 1 H), 4.62 (d, J = 11.3 Hz, 1 H), 4.30 (d, J = 11.3 Hz, 1 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.4, 155.0, 147.4, 146.8, 136.2, 134.8, 133.6, 132.1, 128.7 (2 C), 128.4, 115.3, 115.1 (2 C), 114.7, 114.5, 109.1, 107.6, 101.2, 76.2, 68.1, 55.5 ppm. MS (EI): *m*/*z* (%) = 363 (35) [M^+ + H], 269 (32), 241 (28), 239 (30). HRMS: calcd. for $C_{22}H_{18}O_5$ [M^+ + H] 363.1232, found 363.1241.

4-(1,2,3-Trimethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenol (19jj): Reaction solvent: phenol, PTSA·H_2O (25 mol-%); reaction time: 48 h; eluent: 20% EtOAc/hexane mixture; yield 60%; light yellow viscous liquid. R_f = 0.47 (EtOAc/hexane, 2:3). IR (neat, film): $\tilde{\nu}_{max}$ = 3372, 2935, 1596, 1515, 1484, 1449, 1402, 1322, 1228, 1194 cm^{-1}. ^1H NMR (500 MHz; $CDCl_3$): δ = 7.75 (d, J = 7.7 Hz, 1 H), 7.51–7.47 (m, 1 H), 7.44 (d, J = 7.1 Hz, 1 H), 7.41–7.37 (m, 1 H), 7.24 (s, 1 H), 7.22 (s, 1 H), 6.82 (s, 1 H), 6.80 (s, 1 H), 6.13 (s, 1 H), 5.68 (br. s, 1 H), 5.13 (s, 1 H), 4.66 (d, J = 11.1 Hz, 1 H), 4.30 (d, J = 11.1 Hz, 1 H), 3.93 (s, 3 H), 3.66 (s, 3 H), 3.61 (s, 3 H) ppm. ^{13}C NMR (125 MHz; $CDCl_3$): δ = 155.2, 152.8, 150.3, 142.1, 136.7, 134.8, 134.6, 131.6, 129.8, 129.2, 128.9 (2 C), 128.1, 127.9, 126.4, 115.1 (2 C), 107.8, 75.6, 67.9, 61.0, 60.9, 55.7 ppm. MS (EI): *m*/*z* (%) = 379 (8) [M^+ + H], 349 (100), 255 (18). HRMS: calcd. for $C_{23}H_{22}O_5$ [M^+ + H] 379.1545, found 379.1547.

4-(1,2,3,9-Tetramethoxy-5,7-dihydrodibenzo[*c*,*e*]oxepin-5-yl)phenol (19kj): Reaction solvent: phenol, PTSA·H_2O (25 mol-%); reaction time: 48 h; eluent: 20% EtOAc/hexane mixture; yield 60%; light yellow solid; R_f = 0.37 (EtOAc/hexane, 2:3); m.p. 155–160 °C. IR

(neat, film): $\tilde{\nu}_{max}$ = 3410, 2928, 1609, 1511, 1486, 1452, 1402, 1315, 1240 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 7.68 (d, J = 8.5 Hz, 1 H), 7.24 (s, 1 H), 7.22 (s, 1 H), 7.04 (dd, J = 8.5, 2.5 Hz, 1 H), 6.99 (d, J = 2.5 Hz, 1 H), 6.82 (s, 1 H), 6.79 (s, 1 H), 6.12 (s, 1 H), 5.48 (br. s, 1 H), 5.14 (s, 1 H), 4.60 (d, J = 11.1 Hz, 1 H), 4.29 (d, J = 11.1 Hz, 1 H), 3.92 (s, 3 H), 3.87 (s, 3 H), 3.66 (s, 3 H), 3.60 (s, 3 H) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 159.2, 155.1, 152.4, 150.2, 142.2, 136.3, 134.3, 131.8, 130.9, 128.9 (3 C), 126.4, 115.1 (2 C), 114.1, 114.0, 107.9, 75.8, 68.1, 61.0, 60.8, 55.8, 55.4 ppm. MS (EI): m/z (%) = 431(3) [M^+ + Na], 409 (8) [M^+ + H], 379 (100). HRMS: calcd. for $C_{24}H_{24}O_6$ [M^+ + H] 409.1651, found 409.1656. X-ray crystal structure details: crystallized from EtOAc/hexane, formula: $C_{24}H_{24}O_6$, M = 408.43, colour/shape of crystal: light yellow/needle, crystal size: 0.24 × 0.20 × 0.18 mm, a = 9.8231(3) Å, b = 16.7434(5) Å, c = 12.7590(4) Å, V = 2078.57(11) $Å^3$, $\rho_{calcd.}$ = 1.305 Mg/m^3, μ = 0.094 mm^{-1}, F(000) = 864, Z = 4, T = 173(2) K, 14465 reflections collected, 5017 [R(int) = 0.0685] independent reflections, θ_{max} = 28.00°, 436 refined parameters, maximum/minimum residual electron density: 0.251/–0.203 e $Å^{-3}$, $R1$ = 0.0940, $wR2$ = 0.1113. CCDC-1024804 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Biological Evaluations: Preliminary testing was performed on the seven representative compounds **16be**, **16da**, **16ga**, **16ia**, **17bi**, **17ci** and **19kj**. This included a proliferation assay to determine cell concentrations and viability by using a CASI cell counter and apoptosis assays for nuclear DNA fragmentation quantified by FACS flow cytometric determination. For a full description of the methods involved in the preliminary evaluation of the compounds, see the supporting information of ref.[7e] For details of the synergism experiments between **16da** and vincristine on vincristine-resistant cell lines, please refer to the Supporting Information.

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