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Synthesis of bulky 1,2-dialkoxy- and 1,2,3-trialkoxy-arenes

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ABSTRACT

A large series of bulky 1,2-dialkoxy- and 1,2,3-trialkoxy-benzenes was efficiently prepared via Williamson etherification. Preparation of their contiguous bromine-containing derivatives was also achieved.

1. Introduction

1,2-Dimethoxy- and 1,2,3-trimethoxy-benzene units are present in a variety of organic molecules, which possess interesting chemical and biological properties.[1] For example, many representative members of the naturally occurring isoquinoline alkaloid and flavone families contain the first unit, and some cytotoxic lignans (e.g., podophyllotoxin, steganone), and alkaloids (e.g., reserpine) contain the second. A comprehensive literature survey revealed that the bulk of the starting syntheses of 1,2-di(linear alkoxy)arenes rely heavily on Williamson etherification of catechols or on an oxidation–hydrolysis sequence of 1-alkoxyarene-2-carboxaldehydes and subsequent etherification of the resulting aromatic OH group.[2] However, the few known sterically hindered analogues are prepared by inconvenient procedures or are poorly characterized, and the bulky trialkoxy-arenes are especially less well encountered in the literature and constitute a particular synthetic challenge.

As part of our continuous research focus on polyalkoxy-aryl-containing phosphine ligands for transition metal-catalyzed transformations,[3] we present herein the practical synthesis on a preparative scale of series of bulky 1,2-dialkoxy-benzenes and naphthalenes, and also of isomeric trialkoxy-benzenes.

2. Results and discussion

2.1. Preparation of bulky 1,2-dialkoxy-arenes

A series of 1,2-dialkoxy-benzenes **1a**–**j** was prepared under improved procedures starting from catechol and the appropriate alkyl halide via Williamson etherification in acetone, followed by hydrogenation of the pendent olefinic group when required (Scheme 1, Table 1).[4] Various primary and secondary alkyl groups with branching on the first or second carbon atom were successfully introduced under mild conditions demonstrating the suitability of this method for the incorporation of the relatively sensitive β-methallyl (β-Met), 2-cyclohexenyl (*c*-Hexen-2-yl) and cyclohexyl (Cy) groups, which were appended taking advantage of the corresponding activated halide on allylic position toward nucleophilic substitution, thus avoiding harsh alkylation conditions.[5] Following, PtO_2-catalyzed hydrogenation under low H_2 pressures of the olefinic groups proceeded smoothly but partial over-reduction, i.e., partial hydrogenolysis to the corresponding phenol, occurred at higher H_2 pressures or upon longer exposures. The *o*-alkoxyphenol could be conveniently eliminated from the 1,2-dialkoxy-arene by basic workup (washing with aq NaOH and/or distillation over NaH).

Scheme 1. Preparation of bulky 1,2-dialkoxy-benzenes **1a**–**j**.

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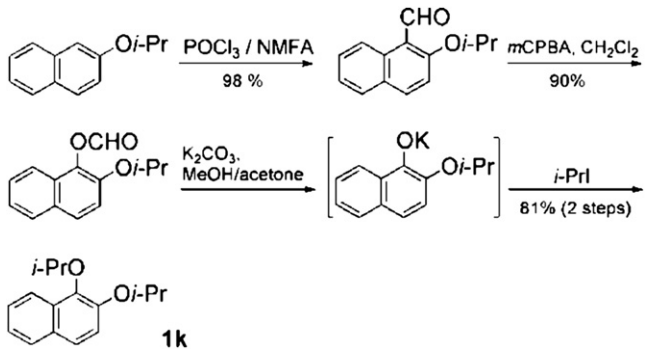
Table 1
Bulky 1,2-dialkoxy-benzenes **1a**–**j** prepared via Scheme 1

1	R^1	R^2	Conditions[a]	Isolated yield %
a	*i*-Pr	H	*i*-PrBr (1 equiv), K_2CO_3 (2.5 equiv), reflux in acetone	88
b	*i*-Pr	*i*-Pr	*i*-PrI (3 equiv), K_2CO_3 (3.5 equiv), reflux in acetone	94
c	*i*-Bu	H	*i*-BuI (1.5 equiv), K_2CO_3 (2.5 equiv), reflux in acetone	80
d	β-Met	β-Met	β-Methallyl chloride (3 equiv), KI (cat.), K_2CO_3 (4 equiv), reflux in acetone	86
e[b]	*i*-Bu	*i*-Bu	H_2 (1 bar), PtO_2 (cat.), rt in EtOH	95
f	$TMSCH_2$	$TMSCH_2$	$TMSCH_2I$ (2.2 equiv), K_2CO_3 (4 equiv), 85 °C in DMF	85
g	Neopentyl	H	*t*-$BuCH_2I$ (2.2 equiv), K_2CO_3 (4 equiv), 90 °C in DMF	67
h	*c*-Pen	*c*-Pen	*c*-PenBr or *c*-PenI (3 equiv), K_2CO_3 (3.5 equiv), reflux in acetone	92
i	*c*-Hexen-2-yl	*c*-Hexen-2-yl	2-Cyclohexenyl bromide[c] (2.5 equiv), K_2CO_3 (3 equiv), rt in acetone	86
j[d]	Cy	Cy	H_2 (1 bar), PtO_2 (cat.), rt in EtOH	86

[a] Reactions were carried out with catechol using the appropriate alkyl halide under the mentioned conditions; the 1,2-dialkoxy-benzenes were distilled and displayed >99% chemical purity by ^{1}H NMR (see Experimental section).
[b] Prepared from **1d**.
[c] Another nomenclature is 3-bromocyclohexene.
[d] Prepared from **1i**.

The nature of both alkyl chain (bulkiness) and halogen atom (especially iodine vs bromine) of the alkyl halide proved to dictate the proper choice of the reaction conditions, which in turn affected the reaction rate and yield. Whereas use of *i*-PrBr (1 equiv) or *i*-BuI (1–2 equiv) furnished mostly the corresponding *o*-alkoxyphenol, *i*-PrI (>2 equiv) afforded the targeted 1,2-diisopropoxybenzene in very high yield (after 2 day reflux in acetone). And while practically no O-alkylation of catechol in acetone in the presence of K_2CO_3 with the bulky neopentyl group occurred, using either its iodide or tosylate, mono-O-alkylation was complete in DMF at 90 °C using the iodide (even with>2 equiv) and O,O′-dialkylation could only be achieved as described in the literature.[4b] By contrast, under the same reaction conditions in DMF, bis($TMSCH_2$)-alkylated product was obtained in good yield using $TMSCH_2I$. As expected, use of *i*-PrI and cyclopentyl iodide (*c*-PenI) in place of the often used corresponding bromides reduced significantly the reaction times. For example, using *i*-PrI led to cleaner and ~twofold faster formation of **1b**.

We were also interested in the preparation of 1,2-diisopropoxynaphthalene (**1k**). Its synthesis was accomplished in a good overall yield (71%) starting from 2-isopropoxynaphthalene as depicted in Scheme 2. Noteworthy, the relatively sensitive formate intermediate ensuant from the Baeyer–Villiger oxidation of the aromatic carboxaldehyde was directly used in the subsequent transformation and its saponified product was O-alkylated in situ.



Scheme 2. Synthesis of 1,2-diisopropoxynaphthalene (**1k**).

2.2. Preparation of 1-bromo-2,3-dialkoxy-arenes

While 1,2-dialkoxy-arenes can be, in general, directly ring *ortho*-lithiated with butyllithiums due to the *ortho*-directing ability of the alkoxy group,[6] the generation of the *ortho*-lithiated species can be conveniently facilitated under mild conditions via bromine–lithium exchange of the suitably-placed bromine atom. This is a must in some problematic cases where the direct *ortho*-lithiation is not complete with remaining transmetallating agent still present in the medium,[7] or when utilizing unsymmetrical 1,2-dialkoxy-arenes with two non-equivalent and competing free *ortho*-positions. In such cases, in order to avoid side reactions from competing different organolithiums with the electrophile, access to the bromo-derivative in a predictable manner is crucial and permits the regioselective formation of the desired aryllithium in high yield.[8]

For example, bromoarenes **2a** and **2b** (Chart 1) were obtained in 56% and 64% isolated yield, respectively, following *o*-lithiation with *n*-BuLi/TMEDA of the corresponding arene and quench with 1,2-dibromoethane. Also, the contiguous bromine atom-containing 1,2-dialkoxy-arenes **2c**–**e** (Scheme 3) were prepared in good yields by etherification of the resulting *o*-bromo-hydroxyarene obtained by *ortho*-regioselective ring bromination (*t*-$BuNH_2/Br_2$[9]) of the *o*-alkoxyphenol.[10] In particular, 3-bromocatechol acetonide (**2c**) was prepared in good overall yield starting from guaiacol. Thus, the 3-bromocatechol derived from 2-hydroxy-3-bromoanisole treatment with BBr_3, furnished **2c** (86% yield) under acid-catalyzed ketalization using PCl_3/acetone in benzene.[11] Such regioselective incorporation of bromine atom at an adjacent requisite position facilitates lithiation or prevents the subsequent lithiation in the 'wrong sense'.[12]

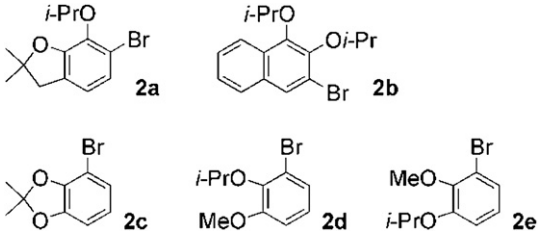
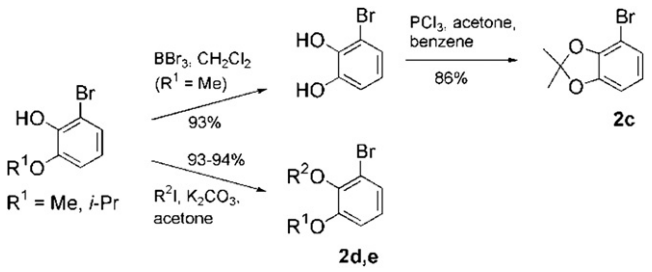


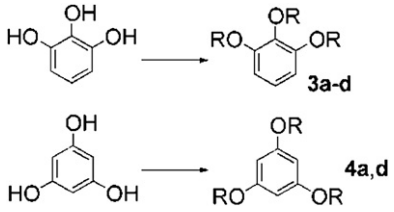
Chart 1. Prepared bromine-containing 1,2-dialkoxy-arenes.



Scheme 3. Synthesis of **2c**–**e**.

2.3. Preparation of bulky isomeric trialkoxy-benzenes

The series of 1,2,3- (**3a**–**d**) and 1,3,5-trialkoxy-benzenes (**4a**,**d**) were prepared starting from pyrogallol and phloroglucinol, respectively, via Williamson etherification with the appropriate alkyl halide (Scheme 4, Table 2). Though pyrogallol is structurally more congested than phloroglucinol, here again various alkyl groups with branching on the first or second carbon atom were successfully incorporated in acetone. Interestingly, while monitoring periodically by ^{1}H NMR the pyrogallol O,O′,O″-trialkylation progress, it was noticed that the unsymmetrical 2,3-dialkoxyphenol (not isolated) was the major intermediate formed and not the expected 2,6-dialkoxyphenol. Electronic effects seem to favor such a situation. In view of the clean formation of 1,2,3-triisopropoxy- (**3a**) and 1,2,3-tricyclopentoxybenzene (**3d**) in high yields, *i*-PrI and *c*-PenBr/*c*-PenI were used, respectively, however still 5–6-day reaction time was required.



Scheme 4. Preparation of bulky 1,2,3- (**3a**–**d**) and 1,3,5-trialkoxy-benzenes (**4a**,**d**).

Table 2
Bulky 1,2,3- (**3a**–**d**) and 1,3,5-trialkoxy-benzenes (**4a**,**d**) prepared via Scheme 4

	R	Conditions[a]	Isolated yield %
3a	*i*-Pr	*i*-PrI (4 equiv), K_2CO_3 (5 equiv), reflux in acetone	91
3b	β-Met	β-Methallyl chloride (5 equiv), KI (cat.), K_2CO_3 (5 equiv), reflux in acetone	95
3c[b]	*i*-Bu	H_2 (1 bar), PtO_2 (cat.), rt in EtOH	79
3d	*c*-Pen	*c*-PenBr (5 equiv), K_2CO_3 (6 equiv), reflux in acetone[c]	76
4a	*i*-Pr	*i*-PrBr (6 equiv), K_2CO_3 (6 equiv), 60 °C in DMF	64
4d	*c*-Pen	*c*-PenBr (6 equiv), K_2CO_3 (6 equiv), 60 °C in DMF	71

[a] Reactions were carried out with pyrogallol or phloroglucinol using the appropriate alkyl halide under the mentioned conditions; the products were distilled and displayed >99% chemical purity by ^{1}H NMR (see Experimental section).
[b] Prepared from **3b**.
[c] *c*-PenI (1 equiv) added after 3 days for higher conversion.

Notably, whereas three β-Met groups were successfully appended to pyrogallol using β-methallyl chloride, resulting in compound **3b** (within 2–3 days), the use of 2-cyclohexenyl bromide led to an unidentifiable complex mixture under various conditions. Also, deprotonation with NaH in THF at 0 °C followed by addition of 2-cyclohexenyl bromide did not improve the latter case in view of the targeted formation of 1,2,3-tri(2-cyclohexenyloxy)benzene. The greater steric demands, reactivity and sensitivity of the 2-cyclohexenyl group seem to prevent this access route. Gratifyingly, the preparation of the 1,2,3-tricyclohexyloxybenzene (**3f**) was cleanly achieved from 1,2-dicyclohexyloxybenzene (**1j**) by stepwise incorporation as outlined in Scheme 5. Thus, the recourse to activated allylic halides allowed the efficient preparation of **3b**,**c**,**e**,**f**. The PtO_2-catalyzed hydrogenation of the pendent olefinic groups in **3b**,**e** proceeded smoothly at 1 bar H_2, however operating at higher H_2 pressures or upon longer exposure times to H_2, partial hydrogenolysis to the phenol occurred as observed with the 1,2-dialkoxy-benzene counterparts.

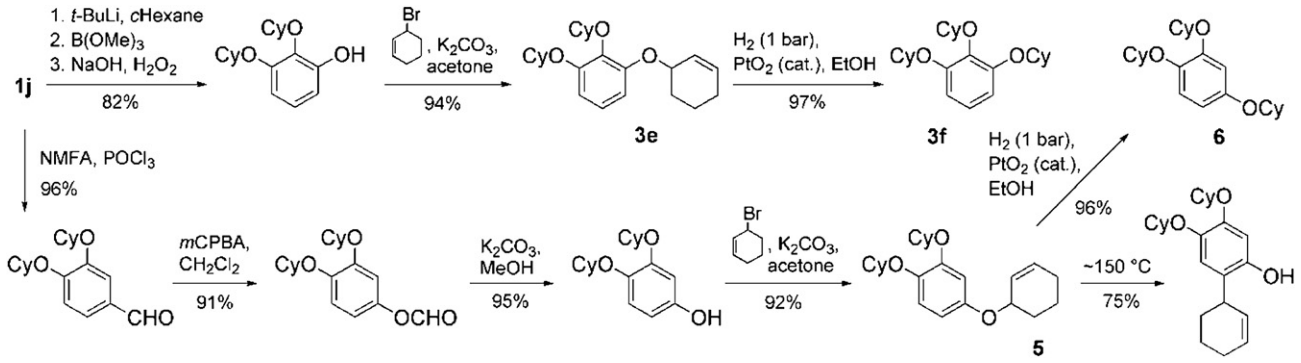
While O,O′,O″-trialkylation of phloroglucinol at 60 °C in DMF using *i*-PrBr afforded the desired compound **4a**,[13] surprisingly no product was formed using *i*-PrI in refluxing acetone. This may be explained by the ability of phloroglucinol to form a keto tautomer under basic conditions.[14]

Further on, 1,2,3-tricyclohexyloxybenzene (**3f**) with its three contiguous and spacially close CyO groups was prepared in an indirect method starting from 1,2-dicyclohexyloxybenzene (**1j**) (Scheme 5). Thus, application of the O-alkylation–hydrogenation sequence on 2,3-dicyclohexyloxyphenol furnished **3f** in 75% overall yield. The 1,2,4-tricyclohexyloxybenzene (**6**) isomer could be prepared from **1j** via formylation under Vilsmeier–Haack conditions (*N*-methylformanilide/$POCl_3$) followed by Baeyer–Villiger oxidation and saponification of the resulting formate, which furnished the 3,4-dicyclohexyloxyphenol. Its O-alkylation with 3-bromocyclohexene afforded **5** in 76% overall yield. Finally, hydrogenation of **5** under 1 bar H_2 provided **6**, while the thermal Claisen rearrangement of **5** led to the 2-(2-cyclohexenyl)-4,5-dicyclohexyloxyphenol.

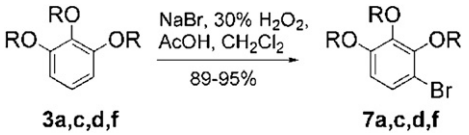
2.3.1. Preparation of 1-bromo-2,3,4-trialkoxy-benzenes. As in the case of 1,2-dialkoxy-arenes, 1,2,3-trialkoxy-arenes can be directly *o*-lithiated with butyllithiums owing to the *ortho*-directing ability of the alkoxy group, though the latter require harsher conditions.[2c,7a] Therefore, the generation of the *ortho*-lithiated species can be facilitated under mild conditions via the bromine–lithium exchange procedure of the suitably-placed bromine atom. The 1-bromo-2,3,4-trialkoxy-benzenes **7a**,**c**,**d**,**f** were conveniently prepared in high yields via an *ortho*-regioselective bromination procedure using NaBr/aq H_2O_2 in acetic acid[15] (Scheme 6).

3. Conclusion

In summary, a large series of bulky 1,2-dialkoxy- and 1,2,3-trialkoxy-benzenes was efficiently prepared. *ortho*-Regioselective incorporation of a bromine atom into these compounds was carried out, which would allow facile generation of the corresponding



Scheme 5. Synthesis of 1,2-dicyclohexyloxybenzene (**1j**) derivatives.



Scheme 6. Bromination of 1,2,3-trialkoxy-benzenes.

aryllithiums under mild conditions. Preparation of some pure isomeric 1,3,5- and 1,2,4-trialkoxy-benzenes was achieved as well. Their application in *P*-stereogenic phosphine synthesis will be communicated in due time.

4. Experimental section

4.1. General considerations

3-Bromocyclohexene (2-cyclohexenyl bromide)[16] and 2,2-dimethyl-2,3-dihydrobenzofuran-7-ol are commercially available. 2-Bromo-6-methoxyphenol and 2-bromo-6-isopropoxyphenol[17] were prepared according to literature. ^{1}H (300 MHz, internal Me_4Si) and ^{13}C (75 MHz, internal $CDCl_3$) NMR spectra were recorded for solutions in $CDCl_3$. IR spectra were recorded using a Specac Golden Gate ATR cell equipped with a diamond crystal.

4.2. Detailed synthetic protocols

*4.2.1. 2-Isopropoxyphenol (**1a**).* A mixture of catechol (11.0 g, 100 mmol), 2-bromopropane (9.40 mL, 100 mmol), and K_2CO_3 (34.5 g, 250 mmol) in acetone (100 mL) was refluxed for 1 day and the reaction progress monitored by TLC. The salts were filtered off rinsing with acetone and the filtrate concentrated. The residue was partitioned between diluted aq HCl (100 mL) and Et_2O (80 mL), and the product extracted with Et_2O (2×80 mL). The organic layer is dried (Na_2SO_4) and concentrated. Kugelrohr distillation (120 °C, 10 mbar) afforded a colorless liquid (13.4 g, 88%); δ_H 1.35 (6H, d, *J* 6.1 Hz, 2Me), 4.56 (1H, sept, *J* 6.1 Hz, CH), 5.77 (1H, s, OH), 6.77–6.96 (4H, m). ^{1}H NMR is in accordance with the literature data.[2b,17c]

*4.2.2. 1,2-Diisopropoxybenzene (**1b**).* A mixture of catechol (11.0 g, 100 mmol), 2-iodopropane (30.0 mL, 300 mmol), and K_2CO_3 (48.5 g, 351 mmol) in acetone (100 mL) was refluxed for 2 days and the reaction progress monitored by TLC. The salts were filtered off rinsing with acetone and the filtrate concentrated. The residue was partitioned between H_2O (100 mL) and Et_2O (80 mL), and the product extracted with Et_2O (2×80 mL). The organic layer was washed with 1 M NaOH (50 mL), dried (Na_2SO_4), and concentrated. Kugelrohr distillation (120 °C, 10 mbar) afforded a colorless liquid (18.3 g, 94%); R_f (toluene) 0.6; δ_H 1.33 (12H, d, *J* 6.1 Hz, 4Me), 4.46 (2H, sept, *J* 6.1 Hz, 2CH), 6.87–6.96 (4H, m); δ_C 22.2, 72.1, 118.4, 121.7, 149.2. ^{1}H NMR is in accordance with the literature data.[18]

*4.2.3. 2-Isobutoxyphenol (**1c**).* Prepared following similar procedure as for **1a** using isobutyl iodide (1-iodo-2-methylpropane) (17.3 mL, 150 mmol, 1.5 equiv) and K_2CO_3 (34.5 g, 250 mmol, 2.5 equiv) refluxing for 3 days. The residue was purified on silica gel eluting with hexane/toluene 95:5 affording a colorless liquid, which solidified upon standing (13.3 g, 80%); mp 50–51 °C; δ_H 1.03 (6H, d, *J* 6.7 Hz, 2Me), 2.11 (1H, tsept, *J* 6.6, 6.7 Hz, CH_2CH), 3.79 (2H, d, *J* 6.6 Hz, CH_2), 5.67 (1H, s, OH), 6.81–6.88 (3H, m), 6.90–6.95 (1H, m); δ_C 19.2, 28.2, 75.1, 111.6, 114.4, 120.0, 121.3, 145.8, 146.0; HRMS (ESI): *m*/*z* calcd for $C_{10}H_{13}O_2$ [M^+–H] 165.092, found 165.091. ^{1}H NMR is in accordance with the literature data.[2a]

*4.2.4. 1,2-Bis(β-methallyloxy)benzene (**1d**).* Prepared following similar procedure as for **1b** using β-methallyl chloride (3-chloro-2-methylpropene) (27.2 g, 300 mmol, 3 equiv), KI (cat.), and K_2CO_3 (55.3 g, 400 mmol, 4 equiv) in acetone (200 mL) refluxing for 2 days. The residue was purified on silica gel eluting with petroleum ether 40–60/EtOAc 9:1 (R_f 0.7) affording a colorless liquid (18.8 g, 86%); ν_{max} 2915, 1592, 1500, 1451, 1247, 1204, 1123 cm^{-1}; δ_H 1.82–1.85 (6H, m, Me), 4.47–4.50 (4H, m, $2CH_2$), 4.95–4.98 (2H, m, $2CH_aH_b$), 5.10–5.12 (2H, m, $2CH_aH_b$), 6.87–6.90 (4H, m); δ_C 19.3, 72.7, 112.3, 114.3, 121.2, 141.0, 148.8; *m*/*z* (ESI) 219.1 (100, MH^+); HRMS (ESI): MH^+, found 219.138. $C_{14}H_{19}O_2$ requires 219.139.

*4.2.5. 1,2-Diisobutoxybenzene (**1e**).* A mixture of **1d** (18.0 g, 82.5 mmol) and PtO_2 (40.0 mg) in EtOH (96%, 75 mL) was hydrogenated with a Parr hydrogenator at rt under 1 bar of H_2 for 2 h. Following, it was filtered through Celite and the filtrate concentrated. Kugelrohr distillation (115 °C, 0.04 mbar) over NaH afforded a faint yellow-colored oil (17.2 g, 95%); R_f (hexane/toluene 1:1) 0.6; ν_{max} 2957, 1592, 1501, 1470, 1452, 1251, 1224, 1121 cm^{-1}; δ_H 1.04 (12H, d, *J* 6.7 Hz, 4Me), 2.12 (2H, tsept, *J* 6.6, 6.7 Hz, 2CH), 3.74 (4H, d, *J* 6.6 Hz, $2CH_2$), 6.85–6.88 (4H, m); δ_C 19.2, 28.4, 75.6, 114.1, 120.9, 149.4; *m*/*z* (ESI) 223.2 (100, MH^+); HRMS (ESI): MH^+, found 223.169. $C_{14}H_{23}O_2$ requires 223.170.

*4.2.6. 1,2-Bis(trimethylsilylmethoxy)benzene (**1f**).* A mixture of catechol (1.10 g, 10.0 mmol), (iodomethyl)trimethylsilane (4.70 g, 22.0 mmol), and K_2CO_3 (5.50 g, 40.0 mmol) in DMF (40 mL) was stirred at 85 °C for 2 days. Following, H_2O (100 mL) was added and the product extracted with Et_2O (3×100 mL). The organic layer was washed with H_2O (4×50 mL), dried (Na_2SO_4), and concentrated affording a brown-colored oil, which was purified on silica gel eluting with hexane/CH_2Cl_2 9:1 (R_f 0.4); colorless liquid (2.40 g, 85%); ν_{max} 2957, 1590, 1497, 1429, 1248, 1231, 1216, 1116 cm^{-1}; δ_H 0.20 (18H, s, 9Me), 3.61 (4H, s, $2CH_2$), 6.87–6.93 (2H, m), 6.96–7.02 (2H, m); δ_C −3.1, 61.4, 112.0, 120.3, 151.5; *m*/*z* (ESI) 283.2 (100, MH^+); HRMS (ESI): MH^+, found 283.155. $C_{14}H_{27}O_2Si_2$ requires 283.155.

*4.2.7. 2-Neopentoxyphenol (**1g**).* Prepared following similar procedure as for **1f** using neopentyl iodide (1-iodo-2,2-dimethylpropane) (2.92 mL, 22.0 mmol, 2.2 equiv) and heating at 90 °C for 3 days. The resulting mixture was diluted with H_2O (50 mL), acidified and extracted with Et_2O (3×10 mL). The organic layer was washed with H_2O (3×10 mL), dried (Na_2SO_4), and concentrated affording a brown oil, which was purified on silica gel eluting with hexane/toluene 9:1 (R_f 0.2): yellowish syrup (1.21 g, 67%); δ_H 1.06 (9H, s, 3Me), 3.68 (2H, s, CH_2), 5.62 (1H, s, OH), 6.81–6.89 (3H, m), 6.91–6.96 (1H, m); δ_C 26.6, 31.9, 78.6, 111.7, 114.4, 120.1, 121.3, 145.8, 146.2; *m*/*z* (ESI) 181.1 (100, MH^+); HRMS (ESI): MH^+, found 181.122. $C_{11}H_{17}O_2$ requires 181.123.

*4.2.8. 1,2-Dicyclopentoxybenzene (**1h**).* Prepared following similar procedure as for **1b** using bromocyclopentane (29.0 mL, 270 mmol, 3 equiv) or iodocyclopentane (3 equiv). Kugelrohr distillation (90 °C, 0.04 mbar) over NaH afforded a colorless liquid (20.4–20.6 g, 92–93%); R_f (toluene) 0.7; ν_{max} 2959, 2971, 1590, 1494, 1452, 1251, 1218, 1168 cm^{-1}; δ_H 1.53–1.66 (4H, m, $2CH_2$), 1.75–1.96 (12H, m, $6CH_2$), 4.71–4.77 (2H, m, 2 OCH), 6.84–6.92 (4H, m); δ_C 23.7, 32.6, 80.8, 116.9, 121.0, 148.8; *m*/*z* (EI) 246 (60, M^+); HRMS (EI): M^+, found 246.163. $C_{16}H_{22}O_2$ requires 246.162.

*4.2.9. 1,2-Di(2-cyclohexenyloxy)benzene (**1i**).* A mixture of catechol (22.0 g, 200 mmol), 2-cyclohexenyl bromide (80.5 g, 0.50 mol, 2.5 equiv), and K_2CO_3 (82.9 g, 0.60 mol, 3 equiv) in acetone

(250 mL) was stirred at rt for 1 day. The salts were filtered off rinsing with acetone and the filtrate concentrated. The residue was partitioned between H_2O (200 mL) and Et_2O (150 mL), and the product extracted with Et_2O (2×150 mL), dried (Na_2SO_4) and concentrated. Kugelrohr distillation (85 °C, 0.04 mbar) afforded a colorless liquid (46.5 g, 86%); R_f (hexane/EtOAc 9:1) 0.5; ν_{max} 2934, 1590, 1492, 1451, 1247, 1205, 1110 cm^{-1}; δ_H 1.60–2.17 (12H, m, $6CH_2$), 4.69–4.75 (2H, m, 2 OCH), 5.85–5.96 (4H, m, 2CH=CH), 6.86–7.00 (4H, m); δ_C 18.9, 19.0, 25.1, 28.49, 28.52, 73.1, 118.75, 118.78, 121.9, 127.0, 131.36, 131.38, 149.23, 149.24; *m/z* (EI) 270 (30, M^+); HRMS (EI): M^+, found 270.163. $C_{18}H_{22}O_2$ requires 270.162.

*4.2.10. 1,2-Dicyclohexyloxybenzene (**1j**).* A mixture of 1,2-di(2-cyclohexenyloxy)benzene (**1i**) (40.5 g, 150 mmol) and PtO_2 (100 mg) in EtOH (96%, 100 mL) was hydrogenated with a Parr hydrogenator at rt under 1 bar of H_2 for 6 h. Following, it was filtered through Celite and the filtrate concentrated. Kugelrohr distillation (130 °C, 0.04 mbar) over NaH afforded a colorless liquid (35.1 g, 86%), which crystallized upon standing; mp 40–42 °C; R_f (toluene/EtOAc 9:1) 0.4; ν_{max} 2933, 1855, 1593, 1492, 1449, 1252, 1204, 1111 cm^{-1}; δ_H 1.27–1.46 (6H, m, $3CH_2$), 1.49–1.71 (6H, m, $3CH_2$), 1.73–1.89 (4H, m, $2CH_2$), 1.91–2.02 (4H, m, $2CH_2$), 4.14–4.24 (2H, m, 2 OCH), 6.85–6.97 (4H, m); δ_C 23.6, 25.6, 31.9, 77.0, 118.4, 121.5, 148.9; *m/z* (EI) 274 (10, M^+); HRMS (EI): M^+, found 274.194. $C_{18}H_{26}O_2$ requires 274.193.

4.2.11. 2-Isopropoxy-1-naphthaldehyde. To a cold (0 °C) mixture of 2-isopropoxynaphthalene[19b] (10.0 g, 53.7 mmol) and *N*-methylformanilide (7.20 mL, 58.0 mmol) was added $POCl_3$ (5.30 mL, 58.0 mmol). Then it was heated at 75 °C for 12 h. The mixture was suspended in 2 M NaOH (90 mL) and extracted with Et_2O (3×100 mL). The organic layer was washed with 1 M HCl (50 mL), dried (Na_2SO_4), filtered through a bed of silica gel, and the filtrate concentrated. Crystallization from hexane afforded yellow crystals (11.3 g, 98%): δ_H 1.42 (6H, d, *J* 6.0 Hz, 2Me), 4.79 (1H, sept, *J* 6.0 Hz, CH), 7.24 (1H, d, *J* 9.2 Hz), 7.39 (1H, ddd, *J* 1.1, 6.9, 7.9 Hz), 7.41 (1H, ddd, *J* 1.5, 7.0, 8.5 Hz), 7.70–7.77 (1H, m), 7.98 (1H, d, *J* 9.2 Hz), 9.25–9.30 (1H, m), 10.89 (1H, s); δ_C 22.2, 72.4, 115.2, 118.0, 124.7, 124.8, 128.1, 128.4, 129.6, 131.6, 137.2, 162.9, 192.5. ^1H NMR is in accordance with the literature data.[19]

4.2.12. 2-Isopropoxy-1-naphthyl formate. To a cold (0 °C) solution of 2-isopropoxy-1-naphthaldehyde (10.0 g, 46.7 mmol) in CH_2Cl_2 (100 mL) was added under stirring *m*-CPBA (70%, 60.7 mmol, 15.0 g). The mixture was stirred at rt for 1 h then concentrated. The residue was triturated with hexane (70 mL), insolubles were filtered off, and the filtrate concentrated yielding the product as a yellow oil (10.2 g, 95%; contains <5% *m*-CBA); δ_H 1.37 (6H, d, *J* 6.1 Hz, 2Me), 4.67 (1H, sept, *J* 6.1 Hz, CH), 7.32 (1H, d, *J* 9.1 Hz), 7.40 (1H, ddd, *J* 1.2, 6.8, 8.2 Hz), 7.51 (1H, ddd, *J* 1.3, 6.8, 8.4 Hz), 7.71–7.76 (1H, m), 7.78–7.82 (1H, m), 7.84–7.88 (1H, m), 8.42 (1H, s, CHO); δ_C 22.2, 72.6, 116.9, 120.2, 124.5, 127.1 (2C), 127.7, 127.9, 129.3, 134.0, 145.8, 159.9; *m/z* (EI) 230 (40, M^+); HRMS (EI): M^+, found 230.094. $C_{14}H_{14}O_3$ requires 230.094.

*4.2.13. 1,2-Diisopropoxynaphthalene (**1k**).* To a solution of 2-isopropoxy-1-naphthyl formate (10.0 g, 43.4 mmol) in acetone/MeOH 8:2 (100 mL) was added K_2CO_3 (12.0 g, 86.8 mmol). The mixture was stirred at rt for 1 h then 2-iodopropane (11.1 g, 65.1 mmol) was added and heated at 75 °C for 3 days. The concentrated residue was partitioned between Et_2O (3×100 mL) and H_2O (200 mL), and the organic layer dried (Na_2SO_4) then concentrated. Kugelrohr distillation (105 °C, 0.04 mbar) afforded a yellow oil (8.60 g, 81%); R_f (hexane/toluene 1:1) 0.6; ν_{max} 2974, 2931, 1594, 1467, 1378, 1371, 1262, 1237, 1106 cm^{-1}; δ_H 1.35 (12H, d, *J* 6.1 Hz, 4Me), 4.64 (1H, sept, *J* 6.1 Hz, OCH), 4.73 (1H, sept, *J* 6.1 Hz, OCH), 7.21 (1H, d, *J* 9.0 Hz), 7.33 (1H, ddd, *J* 1.3, 6.8, 8.2 Hz), 7.42 (1H, ddd, *J* 1.4, 6.8, 8.5 Hz), 7.50–7.54 (1H, m), 7.72–7.76 (1H, m), 8.13–8.18 (1H, m); δ_C 22.5, 22.8, 72.3, 75.1, 119.6, 122.3, 123.4, 124.1, 125.5, 127.3, 130.1, 130.8, 142.8, 146.5; *m/z* (EI) 244 (15, M^+); HRMS (EI): M^+, found 244.147. $C_{16}H_{20}O_2$ requires 244.146.

4.2.14. 7-Isopropoxy-2,2-dimethyl-2,3-dihydrobenzofuran. Prepared following similar procedure as for **1b** from 2,2-dimethyl-2,3-dihydrobenzofuran-7-ol (16.4 g, 100 mmol) and 2-iodopropane (12.0 mL, 0.12 mol). Kugelrohr distillation (70 °C, 0.04 mbar) afforded a colorless liquid (19.2 g, 93%); R_f (toluene/EtOAc 9:1) 0.7; ν_{max} 2974, 1594, 1481, 1459, 1370, 1299, 1261, 1242, 1136, 1111 cm^{-1}; δ_H 1.34 (6H, d, *J* 6.1 Hz, CH*Me*$_2$), 1.49 (6H, s, CMe_2), 3.00 (2H, s, CH_2), 4.58 (1H, sept, *J* 6.1 Hz, OCH), 6.71–6.77 (3H, m); δ_C 22.0, 27.9, 43.0, 71.2, 86.5, 115.9, 117.5, 120.0, 128.3, 142.3, 148.5; *m/z* (ESI) 207 (60, MH^+); HRMS (ESI): MH^+, found 207.138. $C_{13}H_{19}O_2$ requires 207.139.

*4.2.15. 6-Bromo-7-isopropoxy-2,2-dimethyl-2,3-dihydrobenzofuran (**2a**).* To a solution of 7-isopropoxy-2,2-dimethyl-2,3-dihydrobenzofuran (0.62 g, 3.00 mmol) and TMEDA (0.45 mL, 3.00 mmol) in Et_2O (5 mL) was added under stirring *n*-BuLi (2 M in cyclohexane, 1.50 mL, 3.00 mmol). The resulting mixture was stirred at rt for 4 h, cooled to −40 °C and 1,2-dibromoethane (0.26 mL, 3.00 mmol) was added. After stirring at rt overnight, the reaction mixture was quenched with H_2O (1 mL). The residue was partitioned between H_2O (10 mL) and CH_2Cl_2 (10 mL), and the product extracted with CH_2Cl_2 (2×10 mL), dried (Na_2SO_4) and concentrated. Purification on silica gel eluting with hexane/toluene 7:3 afforded a colorless oil (0.48 g, 56%); R_f (hexane/toluene 1:1) 0.4; ν_{max} 2975, 2930, 1589, 1448, 1371, 1313, 1101 cm^{-1}; δ_H 1.32 (6H, d, *J* 6.2 Hz, CH*Me*$_2$), 1.47 (6H, s, CMe_2), 2.94 (2H, d, *J* 1.1 Hz, CH_2), 4.65 (1H, sept, *J* 6.2 Hz, OCH), 6.68 (1H, td, *J* 1.1, 7.9 Hz), 6.96 (1H, d, *J* 7.9 Hz); δ_C 22.4, 28.0, 42.8, 74.9, 88.1, 115.9, 120.0, 124.1, 128.5, 139.5, 151.5; *m/z* (ESI) 285 (25, MH^+); HRMS (ESI): MH^+, found 285.050. $C_{13}H_{18}{}^{79}BrO_2$ requires 285.049.

*4.2.16. 3-Bromo-1,2-diisopropoxynaphthalene (**2b**).* Prepared from 1,2-diisopropoxynaphthalene (**1k**) (4.88 g, 20.0 mmol) following similar procedure as for **2a**. Purification on silica gel eluting with hexane/toluene 8:2 afforded a colorless oil (4.14 g, 64%); R_f (hexane/toluene 1:1) 0.8; δ_H 1.32 and 1.36 (12H, 2d, *J* 6.2 Hz, 4Me), 4.75 and 4.83 (2H, 2sept, *J* 6.2 Hz, 2CH), 7.37–7.49 (2H, m), 7.64–7.70 (1H, m), 7.84 (1H, s), 8.08–8.15 (1H, m); δ_C 22.4, 22.6, 75.1, 75.6, 122.6, 125.77, 125.78, 126.5, 126.8, 130.2, 131.3, 133.6, 143.9, 146.2; *m/z* (EI) 322 (25, M^+); HRMS (EI): M^+, found 322.058. $C_{16}H_{19}{}^{79}BrO_2$ requires 322.057.

4.2.17. 1-Bromo-2,3-dihydroxybenzene (3-bromocatechol). To a cold (−78 °C) solution of 2-bromo-6-methoxyphenol (8.00 g, 39.4 mmol) in dry CH_2Cl_2 (40 mL) was added slowly BBr_3 (1 M in CH_2Cl_2, 43.1 mmol, 43.0 mL). After stirring at rt for 1 h, the mixture was poured onto ice-water, stirred for 30 min and extracted with CH_2Cl_2 (3×30 mL). The organic layer was dried ($MgSO_4$) then concentrated affording the title product as a brownish oil (6.90 g, 93%); R_f (toluene/EtOAc 9:1) 0.2; δ_H 5.60 (1H, br s, OH), 5.69 (1H, br s, OH), 6.72 (1H, dd, *J* 8.1, 8.1 Hz), 6.87 (1H, dd, *J* 1.5, 8.1 Hz), 7.00 (1H, dd, *J* 1.5, 8.1 Hz); δ_C 109.5, 114.9, 121.9, 123.3, 140.3, 144.5. ^1H NMR is in accordance with the literature data.[20]

*4.2.18. 3-Bromo-(isopropylidenedioxy)benzene (**2c**).* To a cold (0 °C) solution of 3-bromocatechol (6.00 g, 31.7 mmol) and acetone (2.80 mL, 38.1 mmol) in benzene (25 mL) was added dropwise PCl_3 (1.11 mL, 12.7 mmol). The reaction mixture was stirred at rt until HCl evolution ceased, then H_2O (100 mL) was added. Extraction with CH_2Cl_2 (3×30 mL), drying (Na_2SO_4), and purification of the residue on silica gel eluting with toluene afforded a colorless oil (6.24 g, 86%); R_f (toluene) 0.5; δ_H 1.72 (6H, s, 2Me), 6.67 (2H, 2d, *J* 4.7 Hz), 6.91 (1H, dd, *J* 4.7, 4.7 Hz); δ_C 25.9, 100.7, 107.5, 118.7, 122.1,

124.3, 145.7, 147.7; *m*/*z* (ESI) 229.0 (100, MH^+); HRMS (ESI): MH^+, found 228.987. $C_9H_{10}{}^{79}BrO_2$ requires 228.986.

*4.2.19. 1-Bromo-2-isopropoxy-3-methoxybenzene (**2d**).* Prepared following similar procedure as for **1b** from 2-bromo-6-methoxyphenol (1.00 g, 4.92 mmol), 2-iodopropane (850 μL, 9.85 mmol, 2 equiv), and K_2CO_3 (1.36 g, 9.85 mmol). Colorless liquid (1.12 g, 93%); R_f (toluene) 0.6; ν_{max} 2976, 1572, 1473, 1450, 1435, 1259, 1232, 1102 cm^{-1}; δ_H 1.33 (6H, d, *J* 6.2 Hz, 2Me), 3.83 (3H, s, OMe), 4.55 (1H, sept, *J* 6.2 Hz, OCH), 6.83 (1H, dd, *J* 1.8, 8.3 Hz), 6.89 (1H, dd, *J* 7.7, 8.3 Hz), 7.13 (1H, dd, *J* 1.8, 7.7 Hz); δ_C 22.5, 56.0, 75.9, 111.6, 118.8, 124.3, 125.0, 144.7, 154.1. ^1H NMR is in accordance with the literature data.[17c]

*4.2.20. 1-Bromo-3-isopropoxy-2-methoxybenzene (**2e**).* Prepared following similar procedure as for **1b** from 2-bromo-6-isopropoxyphenol (6.70 g, 29.0 mmol), MeI (3.60 mL, 58.0 mmol, 2 equiv), and K_2CO_3 (8.00 g, 58.0 mmol, 2 equiv). Colorless liquid (6.7 g, 94%); R_f (hexane/EtOAc 9:1) 0.6; δ_H 1.36 (6H, d, *J* 6.1 Hz, 2Me), 3.86 (3H, s, OMe), 4.54 (1H, sept, *J* 6.1 Hz, OCH), 6.83–6.92 (2H, m), 7.12 (1H, dd, *J* 2.6, 6.9 Hz); δ_C 22.1, 60.4, 71.6, 115.4, 117.9, 124.7, 125.0, 147.8, 152.1; *m*/*z* (ESI) 267.0 (75, MNa^+); HRMS (ESI): MNa^+, found 266.999. $C_{10}H_{13}{}^{79}BrO_2Na$ requires 267.000.

*4.2.21. 1,2,3-Triisopropoxybenzene (**3a**).* A mixture of pyrogallol (25.2 g, 0.20 mol), 2-iodopropane (80 mL, 0.80 mol), and K_2CO_3 (138 g, 1.00 mol) in acetone (300 mL) was refluxed for 5 days monitoring the reaction progress by TLC. The salts were filtered off rinsing with acetone and the filtrate concentrated. The residue was partitioned between H_2O (300 mL) and CH_2Cl_2 (100 mL), and the product extracted with CH_2Cl_2 (2×100 mL), dried (Na_2SO_4), and concentrated. Kugelrohr distillation (125 °C, 10 mbar) afforded a light yellow-colored liquid (45.9 g, 91%); R_f (toluene/EtOAc 9:1) 0.6; ν_{max} 2975, 1584, 1468, 1382, 1372, 1244, 1109 cm^{-1}; δ_H 1.30 (6H, d, *J* 6.2 Hz, 2Me), 1.32 (12H, d, *J* 6.1 Hz, 4Me), 4.33 (1H, sept, *J* 6.2 Hz, OCH), 4.52 (2H, sept, *J* 6.1 Hz, 2 OCH), 6.55 (2H, d, *J* 8.3 Hz), 6.88 (1H, t, *J* 8.3 Hz); δ_C 21.8, 22.3, 70.7, 74.8, 109.3, 122.4, 139.2, 152.2; *m*/*z* (ESI) 253.2 (100, MH^+); HRMS (ESI): MH^+, found 253.180. $C_{15}H_{25}O_3$ requires 253.180.

*4.2.22. 1,2,3-Tris(β-methallyloxy)benzene (**3b**).* Prepared following similar procedure as for **3a** using β-methallyl chloride (3-chloro-2-methylpropene) (22.6 g, 250 mmol, 5 equiv), and KI (85.0 mg) refluxing for 2–3 days. Purification on silica gel eluting with hexane/CH_2Cl_2 8:2 afforded a colorless oil (13.7 g, 95%); R_f (hexane/CH_2Cl_2 7:3) 0.4; ν_{max} 2916, 1598, 1490, 1473, 1451, 1249 cm^{-1}; δ_H 1.82–1.85 (6H, m, 2Me), 1.88–1.91 (3H, m, Me), 4.43–4.46 (6H, m, $3CH_2$), 4.90–4.93 (1H, m, CH), 4.94–4.98 (2H, m, 2CH), 5.08–5.12 (3H, m, 3CH), 6.56 (2H, d, *J* 8.3 Hz), 6.90 (1H, dd, *J* 8.0, 8.6 Hz); δ_C 19.4, 19.7, 72.8, 76.9, 107.4, 112.4, 112.7, 123.2, 138.2, 141.0, 142.3, 153.0; *m*/*z* (ESI) 289.2 (100, MH^+); HRMS (ESI): MH^+, found 289.180. $C_{18}H_{25}O_3$ requires 289.180.

*4.2.23. 1,2,3-Triisobutoxybenzene (**3c**).* A mixture of **3b** (12.0 g, 41.6 mmol) and PtO_2 (35.0 mg) in EtOH (96%, 50 mL) was hydrogenated with a Parr hydrogenator at rt under 1 bar of H_2 for 72 h. Following, it was filtered through Celite and the filtrate concentrated. Kugelrohr distillation (150 °C, 0.04 mbar) over NaH afforded a colorless liquid (9.68 g, 79%); R_f (hexane/toluene 2:8) 0.6; ν_{max} 2957, 1597, 1463, 1250 cm^{-1}; δ_H 1.03 (12H, d, *J* 6.8 Hz, 4Me), 1.04 (6H, d, *J* 6.8 Hz, 2Me), 2.07 (1H, tsept, *J* 6.7, 6.7 Hz, CH), 2.11 (2H, tsept, *J* 6.7, 6.7 Hz, 2CH), 3.73 (4H, d, *J* 6.4 Hz, $2CH_2$), 3.74 (2H, d, *J* 6.4 Hz, CH_2), 6.53 (2H, d, *J* 8.4 Hz), 6.90 (1H, t, *J* 8.4 Hz); δ_C 19.3, 19.4, 28.5, 29.2, 75.4, 79.7, 106.6, 123.1, 138.3, 153.5; *m*/*z* (ESI) 295.2 (100, MH^+); HRMS (ESI): MH^+, found 295.226. $C_{18}H_{31}O_3$ requires 295.227.

*4.2.24. 1,2,3-Tricyclopentoxybenzene (**3d**).* Prepared following similar procedure as for **3a** using bromocyclopentane (21.0 mL, 198 mmol, 5 equiv) refluxing for 6 days (with the addition of 1 equiv of iodocyclopentane after 3 days for higher conversion). Kugelrohr distillation (145 °C, 0.04 mbar) afforded yellowish crystals (10.0 g, 76%); R_f (toluene) 0.7; mp 30–32 °C; ν_{max} 2958, 1593, 1466, 1248, 1167 cm^{-1}; δ_H 1.50–1.69 (8H, m, $4CH_2$), 1.74–1.98 (16H, m, $8CH_2$), 4.66–4.72 (1H, m, CH), 4.72–4.79 (2H, m, 2CH), 6.51 (2H, d, *J* 8.2 Hz), 6.87 (1H, t, *J* 8.2 Hz); δ_C 23.4, 23.7, 32.66, 32.68, 79.9, 84.2, 108.0, 122.4, 138.4, 152.4; *m*/*z* (EI) 330 (15, M^+); HRMS (EI): M^+, found 330.220. $C_{21}H_{30}O_3$ requires 330.219.

*4.2.25. 1,3,5-Triisopropoxybenzene (**4a**).* A mixture of phloroglucinol dihydrate (11.35 g, 70.0 mmol), 2-bromopropane (40.0 mL, 0.42 mol, 6 equiv), and K_2CO_3 (58.0 g, 0.42 mol, 6 equiv) in DMF (150 mL) was heated at 60 °C for 1 day. Following, H_2O (100 mL) was added and the product was extracted with Et_2O (3×100 mL). The organic layer was washed with H_2O (4×50 mL), dried (Na_2SO_4), and concentrated. Purification on silica gel eluting with hexane/CH_2Cl_2 9:1 followed by Kugelrohr distillation (90 °C, 0.04 mbar) afforded a colorless liquid (11.3 g, 64%); ν_{max} 2976, 1588, 1464, 1183, 1147, 1111 cm^{-1}; δ_H 1.310 (18H, d, *J* 6.1 Hz, 6Me), 4.47 (3H, sept, *J* 6.1 Hz, 3OCH), 6.03 (3H, s); δ_C 22.1, 69.7, 96.1, 159.7; *m*/*z* (ESI) 253.2 (100, MH^+); HRMS (ESI): MH^+, found 253.180. $C_{15}H_{25}O_3$ requires 253.180.

*4.2.26. 1,3,5-Tricyclopentoxybenzene (**4d**).* Prepared following similar procedure as for **4a** using bromocyclopentane (32.0 mL, 0.30 mol, 6 equiv) heating for 2 days. Purification on silica gel eluting with hexane/CH_2Cl_2 9:1 followed by Kugelrohr distillation (190 °C, 0.04 mbar) afforded a yellowish liquid (11.7 g, 71%), which crystallized upon standing; mp 31–33 °C; ν_{max} 2962, 1591, 1463, 1349, 1149 cm^{-1}; δ_H 1.51–1.66 (6H, m, $3CH_2$), 1.69–1.96 (18H, m, $9CH_2$), 4.64–4.72 (3H, m, 3 OCH), 5.99 (3H, s); δ_C 24.0, 32.9, 79.2, 95.5, 159.8; *m*/*z* (ESI) 331.2 (100, MH^+); HRMS (ESI): MH^+, found 331.228. $C_{21}H_{31}O_3$ requires 331.227.

4.2.27. 2,3-Dicyclohexyloxyphenol. To a solution of 1,2-dicyclohexyloxybenzene (**1j**) (10.0 g, 36.5 mmol) in cyclohexane (100 mL) was added under stirring *t*-BuLi (1.5 M in pentane, 29.2 mL, 43.8 mmol). The resulting mixture was heated at 60 °C for 4 h, cooled to −30 °C, and $B(OMe)_3$ (8.14 mL, 73.0 mmol) was slowly added. After stirring at rt for 15 min, the reaction mixture was hydrolyzed with 1 M HCl (200 mL), extracted with CH_2Cl_2 (3×50 mL), and dried (Na_2SO_4). The residue was taken in THF (250 mL) and 0.5 M NaOH (150 mL) was added followed by slow addition of 30% aq H_2O_2 (100 mL). The reaction mixture was stirred at rt overnight, cooled to 0 °C and $Na_2S_2O_5$ slowly added portionwise until evolution of oxygen ceased. This was acidified to pH ~2 with 1 M HCl and extracted with CH_2Cl_2 (3×50 mL), dried (Na_2SO_4), and concentrated. Purification on silica gel eluting with hexane/toluene 6:4 afforded a yellowish oil (8.69 g, 82%); R_f (hexane/EtOAc 95:5) 0.4; δ_H 1.13–1.64 (12H, m, $6CH_2$), 1.69–1.85 (4H, m, $2CH_2$), 1.90–2.09 (4H, m, $2CH_2$), 4.20–4.31 (2H, m, 2 OCH), 5.87 (1H, br s, OH), 6.45 (1H, dd, *J* 1.4, 8.4 Hz), 6.55 (1H, dd, *J* 1.4, 8.2 Hz), 6.84 (1H, t, *J* 8.3 Hz); δ_C 23.5, 24.3, 25.4, 25.5, 31.8, 32.8, 75.9, 80.7, 107.1, 107.4, 123.2, 134.3, 150.3, 150.4; *m*/*z* (EI) 290 (50, M^+); HRMS (EI): M^+, found 290.190. $C_{18}H_{26}O_3$ requires 290.188.

*4.2.28. 2,3-Dicyclohexyloxy-(2-cyclohexenyloxy)benzene (**3e**).* Prepared following similar procedure as for **1i** from 2,3-dicyclohexyloxyphenol (8.50 g, 29.3 mmol), 3-bromocyclohexene (7.10 g, 43.9 mmol, 1.5 equiv), and K_2CO_3 (8.10 g, 58.6 mmol, 2 equiv) stirring at rt for 3 days. Kugelrohr distillation (60 °C, 0.04 mbar) afforded a yellow-colored syrup (10.1 g, 94%); R_f (hexane/EtOAc 95:5) 0.4; ν_{max} 2932, 2856, 1583, 1466, 1239 cm^{-1}; δ_H 1.15–1.41 (6H, m, $3CH_2$), 1.45–2.17 (20H, m, $10CH_2$), 4.00–4.10 (1H, m, OCH), 4.17–4.27 (1H, m, OCH), 4.73–4.79 (1H, m, OCH), 5.88–5.92 (2H, m, 2CH), 6.54–6.61 (2H, m), 6.86 (1H, t, *J* 8.2 Hz); δ_C

19.0, 23.8, 24.16, 24.19, 25.1, 25.6, 25.7, 28.5, 31.98, 32.01, 32.69, 32.73, 72.3, 76.6, 80.7, 109.9, 110.0, 122.5, 126.9, 133.4, 139.6, 152.4, 152.5; *m*/*z* (EI) 370 (55, M^+); HRMS (EI): M^+, found 370.252. $C_{24}H_{34}O_3$ requires 370.251.

*4.2.29. 1,2,3-Tricyclohexyloxybenzene (**3f**).* A mixture of **3e** (10.0 g, 27.0 mmol) and PtO_2 (50.0 mg) in EtOH (96%, 50 mL) was hydrogenated with a Parr hydrogenator at rt under 1 bar of H_2 for 1 h. Following, it was filtered through Celite and the filtrate concentrated affording a colorless oil (9.75 g, 97%): ν_{max} 2931, 2855, 1497, 1210, 1166 cm^{-1}; δ_H 1.18–1.65 (18H, m, $9CH_2$), 1.72–1.87 (6H, m, $3CH_2$), 1.91–2.08 (6H, m, $3CH_2$), 4.00–4.11 (1H, m, OCH), 4.17–4.27 (2H, m, 2 OCH), 6.54 (2H, d, *J* 8.3 Hz), 6.84 (1H, t, *J* 8.3 Hz); δ_C 23.7, 24.2, 25.6, 25.7, 32.0, 32.7, 76.5, 80.6, 109.5, 122.4, 139.4, 152.3; *m*/*z* (EI) 372 (25, M^+); HRMS (EI): M^+, found 372.268. $C_{24}H_{36}O_3$ requires 372.266.

4.2.30. 3,4-Dicyclohexyloxybenzaldehyde. To a cold (0 °C) solution of **1j** (14.6 g, 53.4 mmol) in NMFA (8.66 g, 64.1 mmol, 7.91 mL) was added $POCl_3$ (9.83 g, 64.1 mmol, 5.87 mL). After overnight stirring at 70 °C, the reaction was quenched with 2 M NaOH (100 mL) and the product extracted with Et_2O (3×50 mL). The organic layer was dried (Na_2SO_4) and concentrated affording a yellow oil (15.5 g, 96%); R_f (toluene) 0.4; δ_H 1.28–1.47 (6H, m, $3CH_2$), 1.49–1.71 (6H, m, $3CH_2$), 1.74–1.89 (4H, m, $2CH_2$), 1.90–2.03 (4H, m, $2CH_2$), 4.23–4.33 (1H, m, OCH), 4.34–4.44 (1H, m, OCH), 6.99 (1H, d, *J* 8.1 Hz), 7.42 (1H, dd, *J* 2.0, 8.1 Hz), 7.44 (1H, d, *J* 2.0 Hz), 9.82 (1H, s, CHO); δ_C 23.3, 23.4, 25.4, 25.5, 31.4, 31.6, 76.5, 77.2, 114.9, 116.3, 126.2, 129.8, 148.7, 154.8, 190.7; *m*/*z* (EI) 302 (20, M^+); HRMS (EI): M^+, found 302.189. $C_{19}H_{26}O_3$ requires 302.188.

4.2.31. 3,4-Dicyclohexyloxyphenyl formate. To a cold (0 °C) solution of 3,4-dicyclohexyloxybenzaldehyde (15.0 g, 49.6 mmol) in CH_2Cl_2 (100 mL) was added under stirring *m*-CPBA (70%, 64.5 mmol, 15.9 g). The mixture was stirred at rt for 1 h then concentrated. The residue was triturated with hexane (50 mL), insolubles were filtered off, and the filtrate concentrated yielding the product as a yellow oil (14.4 g, 91%); R_f (hexane/EtOAc 9:1) 0.7; ν_{max} 2933, 2857, 1740, 1498, 1210, 1158 cm^{-1}; δ_H 1.24–1.42 (6H, m, $3CH_2$), 1.48–1.65 (6H, m, $3CH_2$), 1.73–1.87 (4H, m, $2CH_2$), 1.89–2.01 (4H, m, $2CH_2$), 4.09–4.25 (2H, m, 2 OCH), 6.64 (1H, dd, *J* 2.6, 8.7 Hz), 6.70 (1H, d, *J* 2.6 Hz), 6.91 (1H, d, *J* 8.7 Hz), 8.28 (1H, s, CHO); δ_C 23.6, 23.7, 25.5, 25.6, 31.7, 32.0, 77.2, 78.1, 110.5, 113.1, 119.1, 144.2, 146.9, 149.8, 159.7; *m*/*z* (ESI) 319.2 (40, MH^+); HRMS (ESI): MH^+, found 319.191. $C_{19}H_{27}O_4$ requires 319.191.

4.2.32. 3,4-Dicyclohexyloxyphenol. To a solution of 3,4-dicyclohexyloxyphenyl formate (14.0 g, 44.0 mmol) in MeOH (100 mL) was added under stirring K_2CO_3 (12.2 g, 88.0 mmol). The mixture was stirred at rt for 1 h, concentrated, and the residue partitioned between H_2O (200 mL) and CH_2Cl_2 (100 mL), and the product extracted with CH_2Cl_2 (2×100 mL). The organic layer was dried (Na_2SO_4), concentrated, and the residue crystallized from hexane to afford a white powder (12.1 g, 95%); R_f (hexane/EtOAc 9:1) 0.3; mp 96–98 °C; ν_{max} 3455, 2935, 2857, 1605, 1508, 1449, 1203, 1168 cm^{-1}; δ_H 1.19–1.37 (6H, m, $3CH_2$), 1.42–1.59 (6H, m, $3CH_2$), 1.70–1.83 (4H, m, $2CH_2$), 1.87–2.01 (4H, m, $2CH_2$), 3.94–4.04 (1H, m, OCH), 4.13–4.23 (1H, m, OCH), 5.88 (1H, br s, OH), 6.29 (1H, dd, *J* 2.9, 8.5 Hz), 6.43 (1H, d, *J* 2.9 Hz), 6.77 (1H, d, *J* 8.5 Hz); δ_C 23.7, 24.0, 25.58, 25.63, 31.8, 32.2, 76.7, 79.4, 104.8, 107.0, 121.4, 141.7, 150.3, 151.4; *m*/*z* (ESI) 291.2 (100, MH^+); HRMS (ESI): MH^+, found 291.195. $C_{18}H_{27}O_3$ requires 291.196.

*4.2.33. 3,4-Dicyclohexyloxy-(2-cyclohexenyloxy)benzene (**5**).* Prepared from 3,4-dicyclohexyloxyphenol (10.0 g, 34.4 mmol) following similar procedure as for **3e** and stirring at rt for 2–3 days. Colorless syrup (11.7 g, 92%); R_f (hexane/EtOAc 7:3) 0.9; ν_{max} 2932, 2855, 1511, 1420, 1182, 1167 cm^{-1}; δ_H 1.21–1.40 (6H, m, $3CH_2$), 1.44–1.67 (7H, m, $3CH_2$, CH), 1.70–2.19 (13H, m, $6CH_2$, CH), 3.96–4.06 (1H, m, OCH), 4.14–4.24 (1H, m, OCH), 4.64–4.71 (1H, m, O*CH*=CH), 5.82–5.89 (1H, m, *CH*=CH), 5.91–5.99 (1H, m, CH=*CH*), 6.41 (1H, dd, *J* 2.8, 8.7 Hz), 6.54 (1H, d, *J* 2.8 Hz), 6.83 (1H, d, *J* 8.7 Hz); δ_C 18.9, 23.6, 23.8, 25.0, 25.6, 25.7, 28.2, 31.83, 31.84, 32.2, 71.2, 76.6, 78.7, 106.6, 106.9, 120.7, 126.5, 131.8, 142.5, 150.3, 151.1; *m*/*z* (ESI) 371.3 (100, MH^+); HRMS (ESI): MH^+, found 371.259. $C_{24}H_{35}O_3$ requires 371.259.

*4.2.34. 1,2,4-Tricyclohexyloxybenzene (**6**).* Prepared from **5** (10.0 g, 27.0 mmol) following similar procedure as for **3f**. Colorless oil (9.65 g, 96%); R_f (toluene) 0.7; ν_{max} 2931, 2855, 1497, 1210, 1167 cm^{-1}; δ_H 1.22–1.64 (18H, m, $9CH_2$), 1.73–1.86 (6H, m, $3CH_2$), 1.90–2.03 (6H, m, $3CH_2$), 3.96–4.06 (1H, m, OCH), 4.05–4.15 (1H, m, OCH), 4.15–4.25 (1H, m, OCH), 6.39 (1H, dd, *J* 2.9, 8.8 Hz), 6.51 (1H, d, *J* 2.9 Hz), 6.82 (1H, d, *J* 8.8 Hz); δ_C 23.8, 23.9, 24.0, 25.6, 25.67, 25.7, 31.97, 31.99, 32.3, 76.1, 76.9, 78.8, 107.1, 107.5, 120.7, 142.6, 150.3, 153.2; *m*/*z* (ESI) 373.3 (40, MH^+); HRMS (ESI): MH^+, found 373.274. $C_{24}H_{37}O_3$ requires 373.274.

4.2.35. 2-(2-Cyclohexenyl)-4,5-dicyclohexyloxyphenol. Heating **5** (1.00 g, 2.70 mmol) at 150 °C for 1–2 h afforded the pure title compound (0.75 g, 75%); R_f (toluene/EtOAc 95:5) 0.5; mp 150–152 °C; δ_H 1.20–1.39 (6H, m, $3CH_2$), 1.42–1.69 (8H, m, $4CH_2$), 1.70–1.85 (5H, m, CH, $2CH_2$), 1.87–2.01 (5H, m, CH, $2CH_2$), 2.06–2.14 (2H, m, CH_2), 3.34–3.46 (1H, m, CH), 3.92–4.05 (1H, m, OCH), 4.08–4.22 (1H, m, OCH), 5.33 (1H, br s, OH), 5.78 (1H, m, CH), 6.00 (1H, m, CH), 6.41 (1H, s), 6.68 (1H, s); δ_C 21.3, 23.7, 24.0, 25.0, 25.6, 25.7, 30.2, 31.9, 32.3, 37.4, 76.8, 79.1, 105.7, 121.9, 122.9, 130.0, 130.6, 141.6, 148.6, 149.1; *m*/*z* (ESI) 371.3 (100, MH^+); HRMS (ESI): MH^+, found 371.259. $C_{24}H_{35}O_3$ requires 371.259.

*4.2.36. 1-Bromo-2,3,4-triisopropoxybenzene (**7a**).* To a mixture of **3a** (5.00 g, 19.8 mmol), NaBr (2.00 g, 19.8 mmol) in acetic acid (20 mL)/CH_2Cl_2 (20 mL) was added dropwise 30% aq H_2O_2 (2.00 mL) at rt and the reaction progress was followed by TLC. After 2 h, H_2O (30 mL) was added and the product extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried (Na_2SO_4), concentrated and the residue purified on silica gel eluting with hexane/toluene 3:2 to afford a colorless liquid (6.23 g, 95%); R_f (hexane/toluene 1:1) 0.5; ν_{max} 2976, 1462, 1434, 1382, 1372, 1103 cm^{-1}; δ_H 1.28 (6H, d, *J* 6.1 Hz, 2Me), 1.31 (6H, d, *J* 6.1 Hz, 2Me), 1.34 (6H, d, *J* 6.1 Hz, 2Me), 4.42 (1H, sept, *J* 6.1 Hz, OCH), 4.50 (1H, sept, *J* 6.1 Hz, OCH), 4.72 (1H, sept, *J* 6.1 Hz, OCH), 6.54 (1H, d, *J* 9.0 Hz), 7.15 (1H, d, *J* 9.0 Hz); δ_C 2.0, 22.4, 22.5, 70.9, 75.5, 75.7, 109.7, 111.1, 126.4, 142.8, 149.8, 152.1; *m*/*z* (EI) 330 (25, M^+); HRMS (EI): M^+, found 330.084. $C_{15}H_{23}{}^{79}BrO_3$ requires 330.083.

*4.2.37. 1-Bromo-2,3,4-triisobutoxybenzene (**7c**).* Prepared from **3c** (5.89 g, 20.0 mmol) following similar procedure as for **7a**. Colorless oil (6.94 g, 93%); R_f (hexane/CH_2Cl_2 85:15) 0.5; δ_H 1.03 (6H, d, *J* 6.8 Hz, 2Me), 1.04 (6H, d, *J* 6.8 Hz, 2Me), 1.06 (6H, d, *J* 6.8 Hz, 2Me), 2.07 (1H, tsept, *J* 6.5, 6.8 Hz, CH), 2.12 (1H, tsept, *J* 6.5, 6.8 Hz, CH), 2.13 (1H, tsept, *J* 6.5, 6.8 Hz, CH), 3.69 (2H, d, *J* 6.5 Hz, CH_2), 3.76 (2H, d, *J* 6.5 Hz, CH_2), 3.81 (2H, d, *J* 6.5 Hz, CH_2), 6.53 (1H, d, *J* 9.0 Hz), 7.15 (1H, d, *J* 9.0 Hz); δ_C 19.28, 19.31, 19.4, 28.4, 29.17, 29.20, 75.3, 80.22, 80.24, 108.5, 109.3, 126.5, 143.2, 150.6, 153.1; *m*/*z* (ESI) 273.1 (30, MH^+); HRMS (ESI): MH^+, found 373.137. $C_{18}H_{30}{}^{79}BrO_3$ requires 373.138.

*4.2.38. 1-Bromo-2,3,4-tricyclopentoxybenzene (**7d**).* Prepared from **3d** (6.61 g, 20.0 mmol) following similar procedure as for **7a**. Colorless liquid (7.29 g, 89%); R_f (hexane/toluene 1:1) 0.7; ν_{max} 2959, 1463, 1432, 1289, 1208 cm^{-1}; δ_H 1.51–1.73 (10H, m, $5CH_2$), 1.76–1.99

(14H, m, $7CH_2$), 4.67–4.74 (1H, m, OCH), 4.74–4.80 (1H, m, OCH), 5.02–5.08 (1H, m, OCH), 6.51 (1H, d, *J* 9.0 Hz), 7.14 (1H, d, *J* 9.0 Hz); δ_C 23.6, 23.7, 24.0, 32.7, 32.8, 80.0, 84.8, 85.2, 109.2, 110.2, 126.3, 142.3, 149.7, 152.3; *m*/*z* (EI) 408 (10, M^+); HRMS (EI): M^+, found 408.131. $C_{21}H_{29}{}^{79}BrO_3$ requires 408.130.

*4.2.39. 1-Bromo-2,3,4-tricyclohexyloxybenzene (**7f**).* Prepared from **3f** (7.45 g, 20.0 mmol) following similar procedure as for **7a**. Colorless oil (8.03 g, 89%); R_f (hexane/EtOAc 95:5) 0.6; ν_{max} 2932, 2856, 1462, 1449, 1434, 1206 cm^{-1}; δ_H 1.16–1.65 (m, 18H; $9CH_2$), 1.71–1.87 (6H, m, $3CH_2$), 1.90–2.06 (6H, m, $3CH_2$), 4.05–4.15 (1H, m, OCH), 4.15–4.25 (1H, m, OCH), 4.31–4.42 (1H, m, OCH), 6.53 (1H, d, *J* 9.3 Hz), 7.13 (1H, d, *J* 9.3 Hz); δ_C 23.8, 24.3, 24.4, 25.56, 25.62, 31.8, 32.67, 32.7, 76.2, 81.1, 81.4, 109.4, 110.7, 126.2, 142.5, 149.6, 151.9; *m*/*z* (EI) 450 (45, M^+); HRMS (EI): M^+, found 450.178. $C_{24}H_{35}{}^{79}BrO_3$ requires 450.177.

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