Copper(I)-Catalyzed Intramolecular C_{aryl}–O Bond-Forming Cyclization for the Synthesis of 1,4-Benzodioxines and Its Application in the Total Synthesis of Sweetening Isovanillins

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Abstract: Various substituted 1,4-benzodioxines were synthesized through an Ullmann-type intramolecular C_{aryl}–O coupling cyclization reaction using a catalytic amount of BINOL–CuI complex. This methodology was successfully utilized as the key step in the total synthesis of isovanillyl sweetening agents 5-(2,3-dihydro-1,4-benzodioxin-2-yl)-2-methoxyphenol and 5-(2,3-dihydro-1,4-benzoxathiin-2-yl)-2-methoxyphenol in 15.8% and 14.85% overall yields in five steps from isovanillin.

Key words: copper catalyst, 1,4-benzodioxines, BINOL ligand, Ullmann-type coupling, C–O bond formation

The 1,4-benzodioxine framework has been noted as present in a variety of biologically active compounds such as piperoxan (**1**) (Figure 1), an α-adrenergic blocking agent with considerable stimulating activity, used to diagnose pheochromocytoma and that also serves as an antihypertension agent.[1] Fluparoxan (**2**) is claimed to have potent antidepressant properties[2] and sinaicitin (**3**) exhibits its significant inhibitory activity against the murinelymphocytic leukaemia P-338 cell line.[3] Americanol A (**4**) and isoamericanol A (**5**) exhibit interesting neurotrophic properties.[4] Silybin (**6**) is a naturally occurring benzodioxine that has stimulating therapeutic applications.[5] Very important isovanillyl sweetening agents **7a** and **7b**,[6] which are 500 times sweeter than sucrose, also contain the 1,4-benzodioxine moiety. These compounds could also be used as intermediates for further synthetic transformations.[7]

General methods for the synthesis of the 1,4-benzodioxine fragment include cyclocondensation of catechol with vicinal dibromide derivative analogues,[8] epichlorohydrin,[9] or chloroacrylonitrile.[10] Another approach uses the cycloaddition of a variety of *o*-quinones with a dienophile, either directly or through a two-step process involving a hetero-Diels–Alder reaction followed by [3,3]-sigmatropic rearrangement.[11] Recently Buchwald et al., reported palladium-catalyzed intramolecular C–O bond formation by employing a di-*tert*-butylphosphinobiaryl ligand for the synthesis of 1,4-benzodioxines.[12] However some of these protocols have some limitations such as the availability of starting materials, harsh reaction conditions, high cost of palladium catalysts, and oxophilicity associated with the phosphine-based ligands. Therefore, there is a need to develop an efficient catalyst for the synthesis of 1,4-benzo-

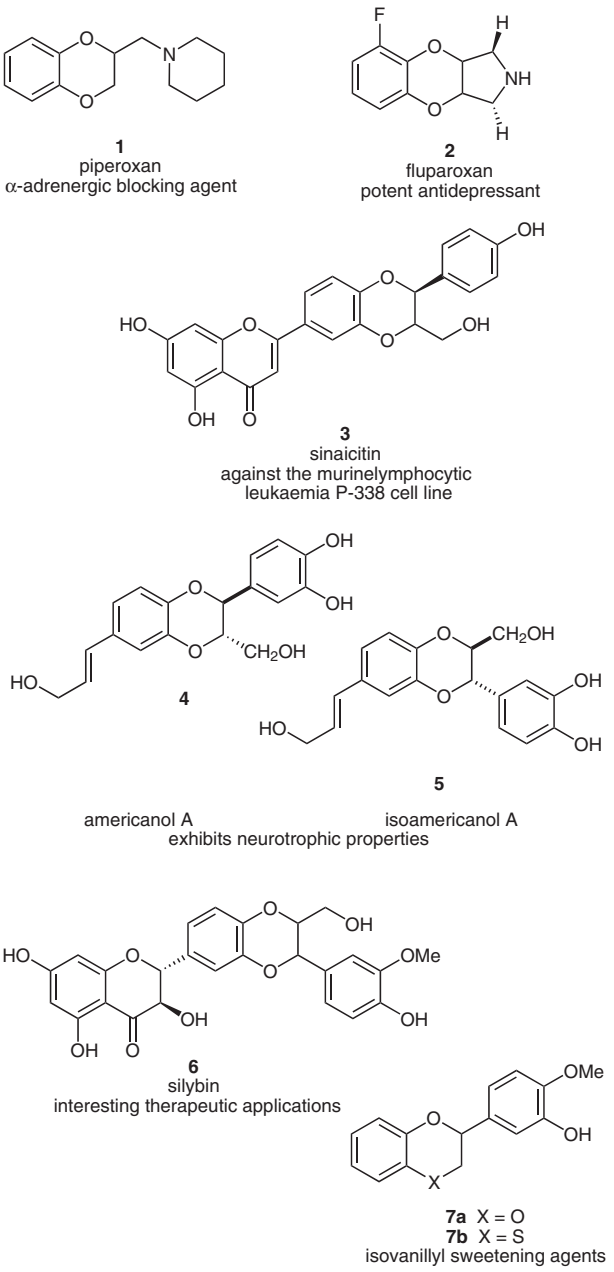

Figure 1 Biologically active compounds containing the 1,4-benzodioxine fragment

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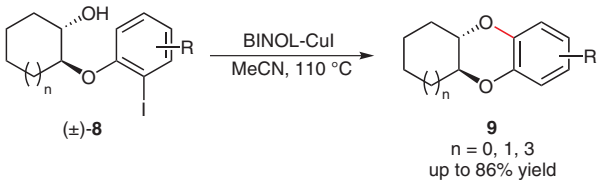
dioxine. In the last decade, several research groups[13] including our research group[14] have developed an efficient catalyst system for the formation of C_{aryl}–X bonds (X = N, O, S, etc.) through copper-catalyzed Ullmann-type coupling between aryl halides and heteroatom-centered nucleophiles. More recently, the Ullmann coupling was successfully extended to the preparation of many heterocycles via copper-mediated cyclization.[15]

Very recently, we have shown that ethylenediamine–CuI is an efficient catalyst system for domino aziridine ring opening followed by Goldberg coupling cyclization in the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines.[16] Due to our continuous interest in this field, herein for the first time we report an easily available BINOL–CuI complex catalyzed synthesis of the racemic 1,4-benzodioxine skeleton **9** through intramolecular C_{aryl}–O bond-forming cyclization from the corresponding 2-(2-iodoaryloxy)alkanol **8** (Scheme 1).



Scheme 1

In preliminary studies, 20 mol% of 1,1′-binaphthyl-2,2′-diamine (BINAM, **L1**; Figure 2) was used as a ligand with 20 mol% of copper(I) iodide for the intramolecular C_{aryl}–O coupling cyclization of 2-(2-iodophenoxy)cyclohexanol (**8a**) in acetonitrile at 110 °C in a sealed tube. Work-up of the reaction after 28 hours furnished 1,4-benzodioxine **9a** in 70% isolated yield (Table 1, entry 1). When the ligand **L1** was replaced by *N*,*N*′-dibenzyl-BINAM (DBBINAM, **L2**), and ligand *N*,*N*′-tetramethyl-BINAM (TMBINAM, **L3**), the coupling reaction afforded 1,4-benzodioxine **9a** in 45% and 38% isolated yields, respectively (entries 7 and 8).

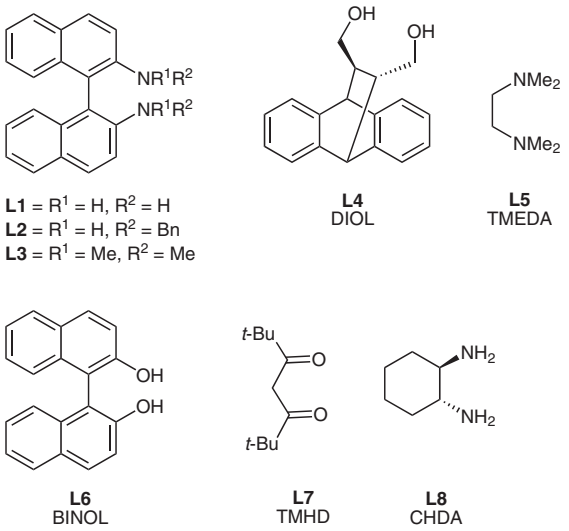
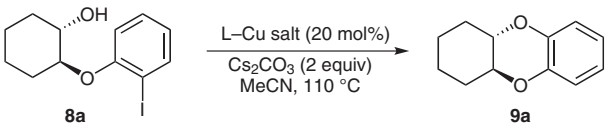


Figure 2

Table 1 Ligand Screening for Intramolecular C_{aryl}–O Bond-Forming Cyclization[a]



Entry	Ligand	Copper salt	Time (h)	Yield[b] (%)
1	BINAM **L1**	CuI	28	70
2	DIOL **L4**	CuI	27	74
3	TMEDA **L5**	CuI	72	45
4	(+)-DET **L9**	CuI	48	38
5	BINOL **L6**	CuI	28	86
6	TMHD **L7**	CuI	48	45
7	DBBINAM **L2**	CuI	36	45
8	TMBINAM **L3**	CuI	36	38
9	CHDA **L8**	CuI	30	59

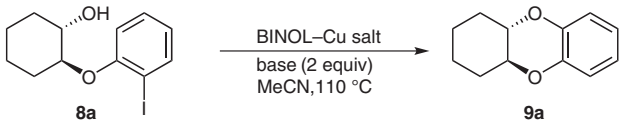
[a] Reactions were carried out in a sealed tube.
[b] Isolated yield.

As anticipated, racemic anthracene-based diol, *trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol (**L4**) gave **9a** in 74% isolated yield in 27 hours (entry 2). Use of BINOL (**L6**) in the place of diol **L4** afforded an excellent yield of 1,4-benzodioxine **9a** with almost the same reaction time (entry 5). However, replacing ligand **L6** by **L5**, **L7**, **L8**, or **L9**, reduced the yield of the coupling product **9a** and the cyclization reaction took much to go to completion (entries 3, 4, 6, and 9). It must be mentioned here that when the reaction was carried out only with copper(I) iodide in the absence of a ligand, the reaction did not provide even a trace amount of coupling product **9a**, which indicates that the ligand is mandatory for the coupling reaction.

Then the reaction was screened with several copper salts, solvents, and bases to optimize the efficiency of the coupling reaction and the results are summarized in Table 2.

Although several copper salts catalyzed the reaction, copper(I) iodide was the copper salt of choice based on the isolated yield of the coupling product (Table 2, entry 1). When the reaction was carried out in other solvents such as dioxane, *N*,*N*-dimethylformamide, dimethyl sulfoxide, etc, the reaction either did not take place or gave a lower yield of 1,4-benzodioxine **9a** (entry 1 vs entries 8–11). Cesium carbonate as base gave the best yields of **9a** in comparison with bases such as tripotassium phosphate and potassium carbonate (entry 1 vs entries 12 and 13). It was also observed that lowering the loading of catalyst BINOL **L6**–CuI complex from 20 mol% of copper(I) iodide and 20 mol% of **L6** to 10 mol% of copper(I) iodide and 10 mol% of **L6** reduced the yield drastically (entry

Table 2 Effect of Copper Salts, Solvents, Bases, and Cu/L Ratio[a]



8a **9a**

Entry	Copper salt	Ratio Cu/L (mol%)	Solvent	Time (h)	Yield[b] (%)
1	CuI	20:20	MeCN	28	86
2	$Cu(OTf)_2$	20:20	MeCN	36	52
3	CuBr	20:20	MeCN	28	83
4	CuCl	20:20	MeCN	28	48
5	$CuCl_2$	20:20	MeCN	48	44
6	$CuSO_4$	20:20	MeCN	48	30
7	$Cu(OAc)_2$	20:20	MeCN	48	38
8	CuI	20:20	DMF	36	42
9	CuI	20:20	toluene	48	32
10	CuI	20:20	1,4-dioxane	28	74
11	CuI	20:20	DMSO	48	52
12	CuI	20:20	MeCN	28	48[c]
13	CuI	20:20	MeCN	28	59[d]
14	CuI	10:10	MeCN	28	49
15	CuI	10:20	MeCN	28	50
16	CuI	5:10	MeCN	28	38
17	CuI	5:10	MeCN	28	55[e]

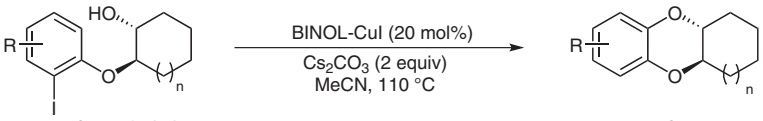
[a] Reactions were carried out in a sealed tube, base was Cs_2CO_3 with a reaction temperature of 110 °C, unless otherwise stated.
[b] Isolated yield.
[c] K_3PO_4 was used as base.
[d] K_2CO_3 was used as base.
[e] Reaction was carried out at 82 °C.

14) and other copper/BINOL ratios also reduced the yields (entries 15–17).

Using these optimized reaction conditions, investigations were initiated into the scope of the BINOL–CuI-catalyzed Ullmann-type intramolecular C_{aryl}–O coupling reaction and the results are summarized in Table 3. Various substituted 2-(2-iodoaryloxy)alkanols **8** reacted to give the corresponding 1,4-benzodioxine skeleton **9** under optimized reaction conditions. When the coupling reaction was carried out with 2-(2-iodophenoxy)cyclohexanol (**8a**), it gave the corresponding 1,4-benzodioxine **9a** with the highest isolated yield of 86% in 28 hours (entry 1). Yields of substituted 1,4-benzodioxines were reduced when an iodobenzene bearing an electron-releasing group, such as a *tert*-butyl group in **8c**, was present (entry 1 vs entry 3). When the reaction was carried out with a strong electron-withdrawing group present, such as the nitro group in **8e**, the reaction failed to give the corresponding benzodioxine (entry 5). However, when the nitro group was replaced with a weak electron-withdrawing group, such as the chloro group in **8d**, the coupling reaction was successful and corresponding benzodioxine **9d** was obtained in 54% isolated yield, though the reaction was somewhat sluggish requiring 40 hours for completion (entry 4).

When 2-(2-iodophenoxy)cyclohexanol (**8a**) was replaced by 2-(2-iodophenoxy)cyclopentanol (**8f**) or unsaturated eight-membered (*Z*)-8-(2-iodophenoxy)cyclooct-4-enol (**8h**), the respective benzodioxines **9f** and **9h** were obtained in 58% and 70% yields, respectively (entry 1 vs entries 6 and 8). Further, alicyclic secondary alcohols **8i** and **8j** successfully underwent intramolecular C_{aryl}–O coupling cyclization reactions to provide the corresponding cyclized products **9i** and **9j** in good yields (entries 9 and 10). It is important to mention that under these optimized conditions, less reactive bromo precursors **10** also provided moderate to good yields of the Ullmann-type intramolecular coupling cyclization products **9** without increasing the catalytic loading and reaction temperature (Table 4).

Table 3 Scope of Intramolecular C_{aryl}–O Coupling Cyclization for the Synthesis of the 1,4-Benzodioxine Moiety[a]



8 n = 0, 1, 3 **9**

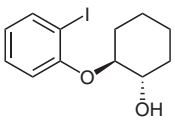
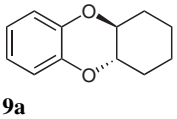
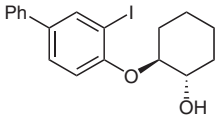
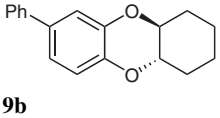
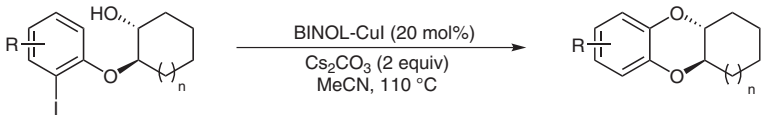
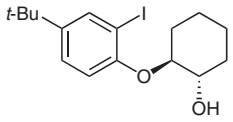
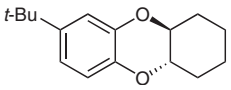
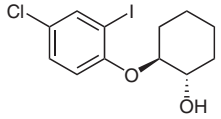
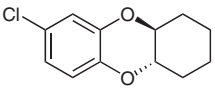
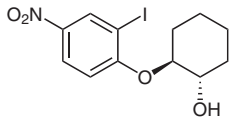
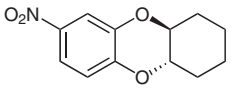
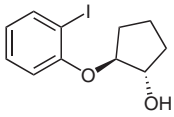
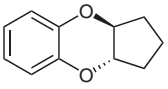
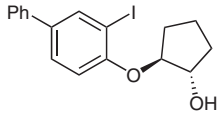
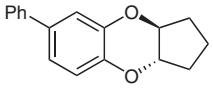
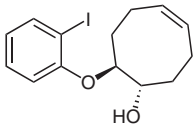
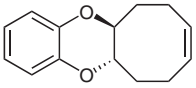
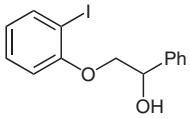
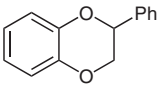
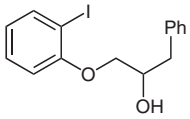
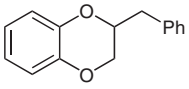
Entry	2-(2-Iodoaryloxy)alkanol	1,4-Benzodioxine	Time (h)	Yield[b] (%)
1	 **8a**	 **9a**	28	86
2	 **8b**	 **9b**	32	83

Table 3 Scope of Intramolecular C_{aryl}–O Coupling Cyclization for the Synthesis of the 1,4-Benzodioxine Moiety[a] (continued)



8 n = 0, 1, 3 **9**

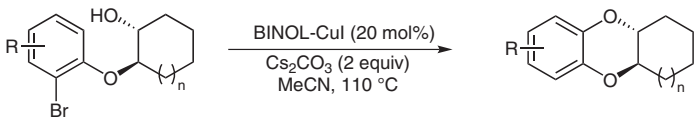
Entry	2-(2-Iodoaryloxy)alkanol	1,4-Benzodioxine	Time (h)	Yield[b] (%)
3	 **8c**	 **9c**	36	73
4	 **8d**	 **9d**	40	54
5	 **8e**	 **9e**	48	00
6	 **8f**	 **9f**	48	58
7	 **8g**	 **9g**	30	72
8	 **8h**	 **9h**	36	70
9	 **8i**	 **9i**	30	74
10	 **8j**	 **9j**	30	73

[a] Reactions were carried out in sealed tube.
[b] Isolated yield.

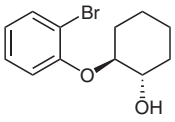
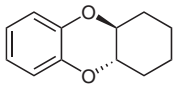
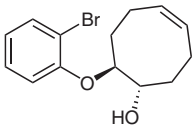
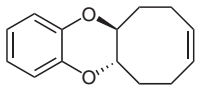
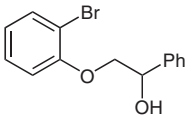
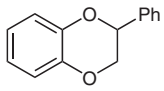
A possible mechanism for the Ullmann-type intramolecular C_{aryl}–O coupling cyclization reaction has been proposed as shown in Scheme 2. Copper(I) oxidatively adds across the aryl–halogen bond of **11** to form the aryl–copper(III) species **12**. Then a nucleophile–halogen exchange takes place to give copper(III) species **13**. This will be followed by reductive elimination of **13** to give the 1,4-benzodioxine moiety **9** and regeneration of the catalytically active copper(I) species for the next catalytic cycle (Scheme 2).

After the development of the BINOL–CuI catalyst for the synthesis of various substituted 1,4-benzodioxines using intramolecular C_{aryl}–O coupling cyclization, the same protocol was successfully applied as a key step for the total

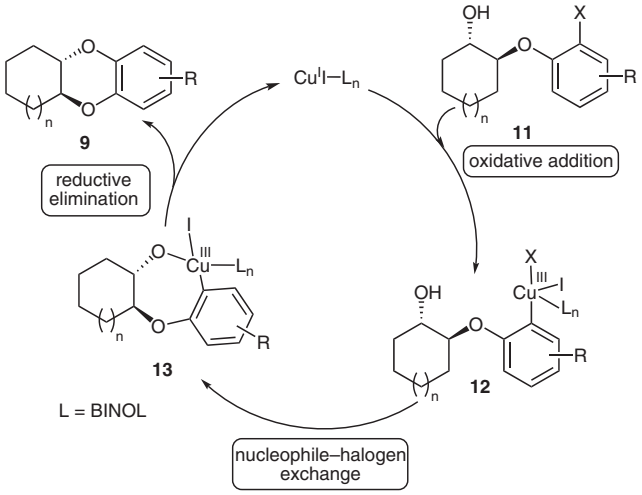
Table 4 BINOL–CuI Complex Catalyzed Synthesis of 1,4-Benzodioxines from 2-(2-Bromophenoxy)alkanols by Ullmann-Type Intramolecular Coupling[a]



10 n = 1, 3 **9**

Entry	2-(2-Bromoaryloxy)alkanol	1,4-Benzodioxine	Time (h)	Yield[b] (%)
1	 **10a**	 **9a**	48	58
2	 **10b**	 **9h**	48	57
3	 **10c**	 **9i**	48	60

[a] Reactions were carried out in sealed tube.
[b] Isolated yield.



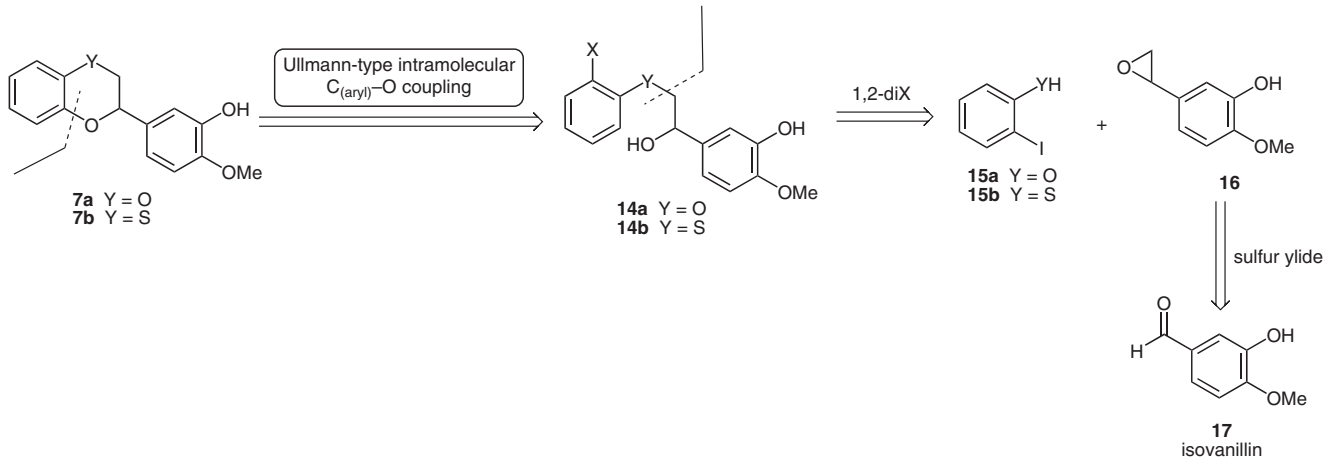
Scheme 2

synthesis of isovanillyl sweetening agents 2,3-dihydro-1,4-benzodioxine **7a** and 2,3-dihydro-1,4-benzoxathiine **7b**.

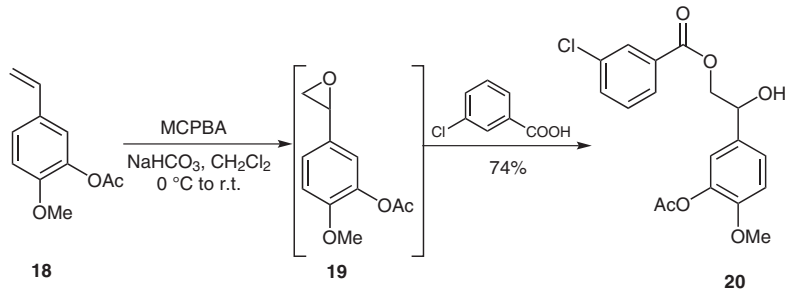
Retrosynthetic analysis for isovanillyl sweeteners **7a**,**b** indicates that they can be synthesized from the secondary alcohols **14a**,**b** by Ullmann-type intramolecular coupling reaction through C_{aryl}–O bond-forming cyclization (Scheme 3). Compounds **14a**,**b** can be synthesized by S_N2 ring opening of epoxide **16** with nucleophiles such as 2-iodophenol (**15a**) or 2-iodothiophenol (**15b**) in the presence of a base. Epoxide **16** can be obtained from the readily available starting material isovanillin (**17**) using a sulfur ylide. This synthetic route involves only three steps from commercially available isovanillin (**17**) with our BINOL–CuI-catalyzed intramolecular coupling cyclization as the key step.

Readily available isovanillin (**17**) on acylation using acetyl chloride with catalytic amount of 4-(dimethylamino)pyridine and pyridine in dichloromethane at room temperature gave the corresponding acetylated product **21** in 96% yield (Scheme 5). Attempted conversion of aldehyde **21** into epoxide **19** using a sulfur ylide failed under several different reaction conditions.

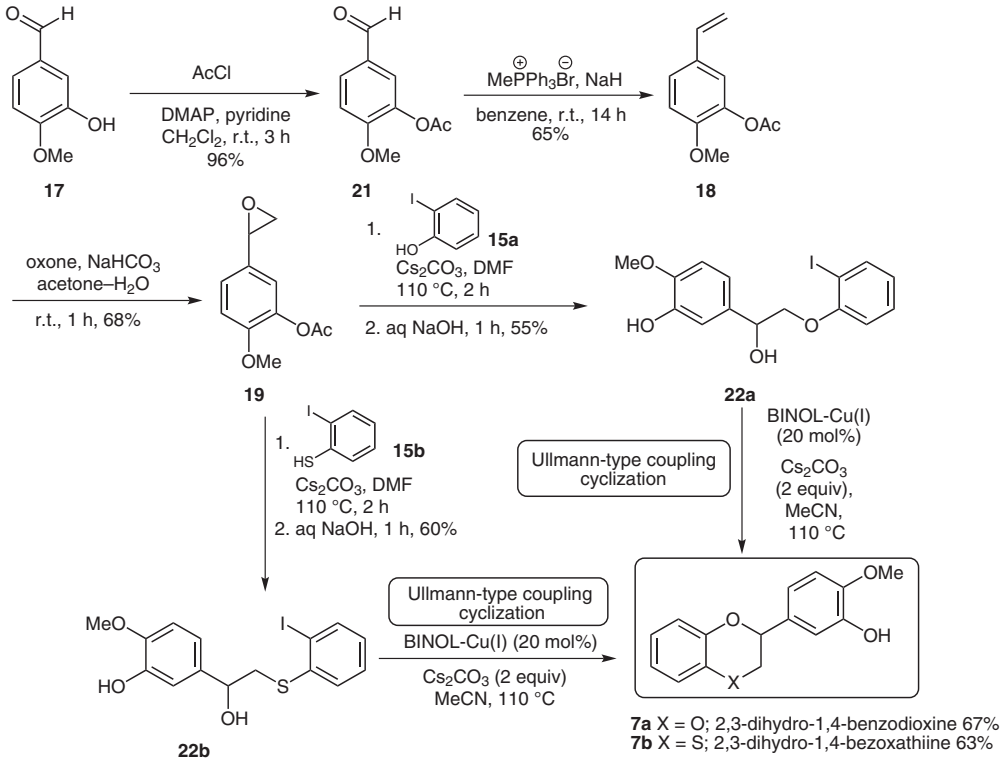
However, the epoxide **19** could be synthesized by an alternative route in two steps as shown in Scheme 5. Wittig olefination of aldehyde **21** gave olefin **18** in 65% isolated yield. When the epoxidation reaction of terminal olefin **18** with 3-chloroperoxybenzoic acid was carried out, it did not stop with the epoxide formation stage and the epoxide-opened product **20** was obtained. In this reaction, epoxide **19** was immediately opened by the byproduct 3-chlorobenzoic acid (Scheme 4). Several attempts to open the in situ generated epoxide by nucleophiles **15a**,**b** failed to give the expected products **22a**,**b**. Finally the Shi epoxidation of terminal olefin **18** gave the epoxide **19** in 68% isolated yield. The epoxide **19** was opened with 2-iodophenol (**15a**) or 2-iodothiophenol (**15b**) using cesium carbonate in *N*,*N*-dimethylformamide solvent at 110 °C to give the required epoxide-opened products **22a** and **22b**, which are the required starting materials for the synthesis of isovanillyl sweeteners 1,4-benzodioxine **7a** and 1,4-benzoxathiine **7b**.



Scheme 3 Retrosynthetic analysis of isovanillyl sweeteners **7a**,**b**



Scheme 4 Epoxidation of olefin with 3-chloroperoxybenzoic acid gives product **20**



Scheme 5 Total synthesis of isovanillyl sweeteners using copper(I)-catalyzed coupling cyclization as the key step

The final key step through Ullmann-type intramolecular C_{aryl}–O coupling cyclization was carried out using 20 mol% BINOL–CuI and cesium carbonate as base in acetonitrile solvent at 110 °C and the reaction provided the target molecule isovanillyl sweetening agents 2,3-dihydro-1,4-benzodioxine **7a** and 2,3-dihydro-1,4-benzoxathiine **7b** in good yields (Scheme 5). An overall yields of 15.8% and 14.85% were obtained for the synthesis of **7a** and **7b**, respectively. It is very important to note that this is the second and easiest method for the total synthesis of isovanillyl sweeteners **7a** and **7b**.

In summary, a new, efficient, experimentally simple, and economically attractive copper(I)–BINOL catalyzed Ullmann-type intramolecular C_{aryl}–O bond-forming coupling cyclization has been developed for the synthesis of a variety of 1,4-benzodioxines from the corresponding 2-(2-iodoaryloxy)alkanols. Less reactive bromo precursors were also used for the synthesis of 1,4-benzodioxines under the same reaction conditions without increasing the reaction temperature and catalyst loading. Using this protocol as a key step, the second and easiest total syntheses of two important isovanillyl sweeteners 2,3-dihydro-1,4-benzodioxine **7a** and 2,3-dihydro-1,4-benzoxathiine **7b** were successfully completed.

All reactions were carried out in sealed tubes under nitrogen atmosphere. All other reagents are commercially available and used without further purification. *o*-Iodophenol, *o*-bromophenol, cyclohexene oxide and cyclopentene oxide were purchased from Sigma-Aldrich company. 4-Chloro-2-iodophenol, 2-iodo-4-*tert*-butylphenol, 2-iodo-4-phenylphenol, 2-iodo-4-nitrophenol were prepared by a literature procedure.[17] Thin-layer chromatography (TLC) was performed using precoated silica gel 60 F254 plates (0.25 mm) which were visualized using a UV fluorescent lamp. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument. ^{1}H NMR spectra are reported relative to TMS (δ = 0.0 ppm) or residual $CDCl_3$ (δ = 7.26 ppm). ^{13}C NMR spectra are reported relative to $CHCl_3$ (δ = 77.16 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrophotometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were recorded on a Micromass Q-Tof mass spectrometer.

2-(2-Iodophenoxy)cyclohexanol (8a); Typical Procedure

Cyclohexene oxide (2.43 g, 24 mmol), 2-iodophenol (4.4 g, 20 mmol), and Cs_2CO_3 (1.9 g, 60 mmol) were added to a 250-mL 2 neck round-bottom flask equipped with a condenser and septum. DMF (12 mL) was added to the contents of the round-bottom flask and the mixture was refluxed at 110 °C for 24 h. The mixture was then allowed to cool to r.t. and washed with EtOAc and H_2O. The organic layer was dried (anhyd Na_2SO_4) and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (silica gel, EtOAc–hexanes) to give **8a** (5.0 g, 80%) as a brown oil; R_f = 0.33 (hexanes–EtOAc, 90:10).

FT-IR (neat): 648, 748, 1017, 1242, 2861, 2936, 3059, 3399 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.56 (m, 4 H), 1.70–1.90 (m, 2 H), 2.10–2.23 (m, 2 H), 2.97 (br s, 1 H), 3.84–3.92 (m, 1 H), 4.02–4.10 (m, 1 H), 6.73–6.78 (m, 1 H), 6.93–6.97 (m, 1 H), 7.28–7.33 (m, 1 H), 7.80 (dd, *J* = 1.6, 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 24.0, 29.7, 31.9, 73.3, 84.5, 88.6, 114.8, 123.2, 129.6, 139.5, 156.8.

HRMS: *m*/*z* [M + H_2O] calcd for $C_{12}H_{17}IO_3$: 336.0222; found: 336.0229.

2-(3-Iodobiphenyl-4-yloxy)cyclohexanol (8b)

Light-brown oil; R_f = 0.43 (hexanes–EtOAc, 90:10).

FT-IR (neat): 699, 739, 1022, 1266, 2863, 2939, 2985, 3051, 3587 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09–1.40 (m, 4 H), 1.60–1.70 (m, 2 H), 1.99–2.10 (m, 2 H), 2.95 (br s, 1 H), 3.71–3.78 (m, 1 H), 3.90–3.99 (m, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 7.18–7.24 (m, 1 H), 7.29 (t, *J* = 7.6 Hz, 2 H), 7.34–7.41 (m, 3 H), 7.88 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 24.0, 29.6, 31.9, 73.2, 84.5, 89.0, 114.7, 126.8, 127.3, 128.1, 128.9, 136.3, 137.9, 139.2, 156.2.

HRMS: *m*/*z* [M + H_2O] calcd for $C_{18}H_{21}IO_3$: 412.0535; found: 412.0539.

2-(4-*tert*-Butyl-2-iodophenoxy)cyclohexanol (8c)

Colorless oil; R_f = 0.43 (hexanes–EtOAc, 90:10).

FT-IR (neat): 705, 739, 1041, 1203, 2865, 2962, 3049, 3581 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.36 (m, 10 H), 1.36–1.49 (m, 3 H), 1.65–1.76 (m, 2 H), 2.03–2.16 (m, 2 H), 3.41 (br s, 1 H), 3.72–4.10 (m, 2 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 7.28 (d, *J* = 8.8 Hz, 1 H), 7.76 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 24.1, 29.8, 31.5, 31.9, 34.2, 73.3, 84.7, 88.5, 114.3, 126.5, 136.5, 146.3, 154.6.

2-(4-Chloro-2-iodophenoxy)cyclohexanol (8d)

Colorless oil; R_f = 0.46 (hexanes–EtOAc, 90:10).

FT-IR (neat): 687, 738, 1034, 1240, 2861, 2936, 3237 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47–1.73 (m, 5 H), 1.93–2.03 (m, 3 H), 3.95 (br s, 1 H), 4.12–4.22 (m, 1 H), 4.31–4.42 (m, 1 H), 6.63–6.74 (m, 1 H), 7.04–7.09 (m, 1 H), 7.56 (d, *J* = 2.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 29.8, 32.8, 77.3, 86.3, 114.1, 116.9, 129.3, 129.4, 137.6, 138.7, 155.0.

MS (EI): *m*/*z* = 352 (M^+).

2-(2-Iodophenoxy)cyclopentanol (8f)

Colorless oil; R_f = 0.40 (hexanes–EtOAc, 90:10).

FT-IR (neat): 648, 748, 1017, 1275, 2932, 3359 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55–1.62 (m, 1 H), 1.71–1.84 (m, 3 H), 2.02–2.15 (m, 2 H), 4.28–4.34 (m, 1 H), 4.46–4.51 (m, 1 H), 6.63 (td, *J* = 1.6, 7.8, 7.6 Hz, 1 H), 6.82 (dd, *J* = 1.2, 8.2 Hz, 1 H), 7.18–7.23 (m, 1 H), 7.69 (dd, *J* = 1.6, 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 29.9, 32.8, 77.4, 86.0, 87.8, 113.9, 122.8, 129.5, 139.7, 156.7.

HRMS: *m*/*z* [M + Na^+] calcd for $C_{11}H_{13}INaO_2$: 326.9858; found: 326.9864.

2-(3-Iodobiphenyl-4-yloxy)cyclopentanol (8g)

Yellow semisolid; R_f = 0.33 (hexanes–EtOAc, 90:10).

FT-IR (neat): 697, 760, 1037, 1245, 2944, 3029, 3055, 3373 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.20 (m, 1 H), 1.52–1.61 (m, 1 H), 1.70–1.84 (m, 2 H), 2.02–2.14 (m, 2 H), 4.26–4.36 (m, 1 H), 4.50 (dd, *J* = 3.2, 6.0 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 1 H), 7.18–7.25 (m, 1 H), 7.27–7.35 (m, 2 H), 7.36–7.47 (m, 3 H), 7.90 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.4, 32.7, 60.6, 86.0, 88.1, 113.7, 126.8, 127.2, 128.1, 128.9, 135.9, 138.0, 139.3, 156.0.

HRMS: *m*/*z* [M + Na^+] calcd for $C_{17}H_{17}INaO_2$: 403.0171; found: 403.0178.

(*Z*)-8-(2-Iodophenoxy)cyclooct-4-enol (8h)
Colorless oil; R_f = 0.40 (hexanes–EtOAc, 90:10).

FT-IR (neat): 635, 786, 1048, 1240, 2907, 2984, 3538 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.64–1.84 (m, 2 H), 2.01–2.27 (m, 4 H), 2.31–2.57 (m, 2 H), 2.93 (br s, 1 H), 4.03–4.12 (m, 1 H), 4.33–4.41 (m, 1 H), 5.51–5.67 (m, 2 H), 6.64 (td, *J* = 1.2, 7.6, 7.6 Hz, 1 H), 6.74–6.79 (m, 1 H), 7.18–7.23 (m, 1 H), 7.68 (dd, *J* = 1.6, 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0, 23.4, 29.1, 31.9, 72.8, 83.2, 88.2, 114.1, 123.1, 128.5, 129.6, 130.0, 139.6, 156.4.

HRMS: *m*/*z* [M + H^+] calcd for $C_{14}H_{18}IO_2$: 345.0352; found: 345.0380.

2-(2-Iodophenoxy)-1-phenylethanol (8i)
Colorless oil; R_f = 0.6 (hexanes–EtOAc, 90:10).

FT-IR (neat): 699, 737, 1018, 1272, 2856, 2923, 3384 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.05 (t, *J* = 9.2 Hz, 1 H), 4.24 (dd, *J* = 3.2, 9.2 Hz, 1 H), 5.24 (dd, *J* = 3.2, 8.6 Hz, 1 H), 6.76–6.88 (m, 2 H), 7.25–7.59 (m, 6 H), 7.83 (dd, *J* = 1.6, 7.8, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.5, 74.9, 87.0, 112.8, 123.4, 126.5, 128.4, 128.7, 129.7, 139.3, 139.5, 156.9.

1-(2-Iodophenoxy)-3-phenylpropan-2-ol (8j)
Brown oil; R_f = 0.36 (hexanes–EtOAc, 80:20).

FT-IR (neat): 700, 730, 1017, 1245, 2922, 3412 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.94 (dd, *J* = 2.4, 6.6 Hz, 2 H), 3.82 (dd, *J* = 6.0, 9.2 Hz, 1 H), 3.95 (dd, *J* = 3.6, 9.2 Hz, 1 H), 4.15–4.24 (m, 1 H), 6.63–6.73 (m, 2 H), 7.12–7.30 (m, 6 H), 7.69 (dd, *J* = 1.6, 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.9, 71.2, 72.2, 86.9, 112.6, 123.2, 126.8, 128.7, 129.5, 129.7, 137.7, 139.5, 156.9.

HRMS: *m*/*z* [M + H^+] calcd for $C_{15}H_{16}IO_2$: 355.0195; found: 355.0199.

2-(2-Bromophenoxy)cyclohexanol (10a)
Colorless oil; R_f = 0.36 (hexanes–EtOAc, 90:10).

FT-IR (neat): 660, 742, 1027, 1242, 2861, 2937, 3406 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.08–1.38 (m, 4 H), 1.53–1.68 (m, 2 H), 1.93–2.03 (m, 2 H), 3.14 (br s, 1 H), 3.64–3.73 (m, 1 H), 3.85–3.94 (m, 1 H), 6.71 (t, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 7.10 (t, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 23.8, 29.4, 31.8, 72.9, 84.2, 113.7, 116.2, 122.4, 128.4, 133.3, 154.5.

HRMS: *m*/*z* [M + Na^+] calcd for $C_{12}H_{15}BrNaO_2$: 293.0153; found: 293.0150.

(*Z*)-8-(2-Bromophenoxy)cyclooct-4-enol (10b)
Colorless oil; R_f = 0.63 (hexanes–EtOAc, 90:10).

FT-IR (neat): 660, 743, 1022, 1239, 2878, 2929, 3011, 3558 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.64–1.86 (m, 2 H), 2.03–2.28 (m, 4 H), 2.31–2.57 (m, 2 H), 4.06 (td, *J* = 4.0, 8.4, 8.2 Hz, 1 H), 4.35 (td, *J* = 3.6, 8.4, 8.4 Hz, 1 H), 5.51–5.73 (m, 2 H), 6.70–6.97 (m, 2 H), 7.11–7.22 (m, 1 H), 7.36–7.50 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 23.4, 29.3, 32.0, 72.9, 83.6, 115.6, 116.3, 122.6, 128.7, 129.3, 130.1, 133.6, 155.0.

2-(2-Bromophenoxy)-1-phenylethanol (10c)
Colorless oil; R_f = 0.56 (hexanes–EtOAc, 90:10).

FT-IR (neat): 666, 700, 1053, 1246, 3060, 3574 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.07 (br s, 1 H), 3.91 (t, *J* = 9.2 Hz, 1 H), 4.08 (dd, *J* = 3.2, 9.6 Hz, 1 H), 5.07 (d, *J* = 8.4 Hz, 1 H), 6.74–6.80 (m, 2 H), 7.11–7.16 (m, 1 H), 7.21–7.33 (m, 3 H), 7.35–7.40 (m, 2 H), 7.43–7.48 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.4, 74.8, 112.5, 113.9, 122.7, 126.4, 128.3, 128.7, 133.5, 139.4, 154.8.

MS (EI): *m*/*z* = 293 (M^+).

1,2,3,4,4a,10a-Hexahydrodibenzo[*b*,*e*][1,4]dioxine[18] (9a); Typical Procedure
2-(2-Iodophenoxy)cyclohexanol (**8**, 159 mg, 0.50 mmol), BINOL (**L6**, 28.6 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and Cs_2CO_3 (325 mg, 1.0 mmol) were added to a sealed tube and this was equipped with screw cap. The sealed tube was evacuated and backfilled with N_2. MeCN (2 mL) was added to the mixture at r.t. and the mixture was heated at 110 °C for 28 h. After complete disappearance of **8** (TLC monitoring), the mixture was allowed to cool to r.t., and the solvent was removed by evaporation. The crude residue was purified by column chromatography (silica gel, EtOAc–hexanes) to afford **9a** (81.7 mg, 86%) as a white solid; mp 43–45 °C (Lit. 43–44 °C); R_f = 0.8 (hexanes–EtOAc, 95:5).

FT-IR (neat): 659, 735, 1264, 2868, 2946, 3049 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.54 (m, 4 H), 1.79–1.91 (m, 2 H), 2.20–2.29 (m, 2 H), 3.68–3.76 (m, 2 H), 6.80–6.90 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 30.3, 76.7, 117.1, 121.4, 144.0.

HRMS: *m*/*z* [M + Na^+] calcd for $C_{12}H_{14}NaO_2$: 213.0891; found: 213.0886.

7-Phenyl-1,2,3,4,4a,10a-hexahydrodibenzo[*b*,*e*][1,4]dioxine (9b)
White solid; mp 135 °C; R_f = 0.66 (hexanes–EtOAc, 95:5).

FT-IR (neat): 693, 752, 1238, 2862, 2940, 3032 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36–1.59 (m, 4 H), 1.81–1.93 (m, 2 H), 2.23–2.33 (m, 2 H), 3.73–3.82 (m, 2 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 7.12 (dd, *J* = 2.4, 8.4 Hz, 1 H), 7.18 (d, *J* = 2.0 Hz, 1 H), 7.32 (t, *J* = 7.2 Hz, 1 H), 7.39–7.46 (m, 2 H), 7.54–7.60 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 30.2, 76.7, 76.8, 115.6, 117.3, 120.1, 126.8, 126.8, 128.5, 128.8, 134.6, 140.8, 143.5, 144.0.

HRMS: *m*/*z* [M + H^+] calcd for $C_{18}H_{19}O_2$: 267.1385; found: 267.1381.

7-*tert*-Butyl-1,2,3,4,4a,10a-hexahydrodibenzo[*b*,*e*][1,4]dioxine[15h] (9c)
White solid; mp 132–133 °C (Lit. 130–131 °C); R_f = 0.80 (hexanes–EtOAc, 95:5).

FT-IR (neat): 704, 733, 1265, 2864, 2947 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9 H), 1.39–1.50 (m, 4 H), 1.82–1.87 (m, 2 H), 2.20–2.27 (m, 2 H), 3.69–3.76 (m, 2 H), 6.81 (d, *J* = 8.8 Hz, 1 H), 6.88 (dd, *J* = 2.4, 8.6 Hz, 1 H), 6.93 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 30.3, 31.6, 34.3, 76.6, 76.7, 114.1, 116.4, 118.3, 141.5, 143.1, 144.7.

MS (EI): *m*/*z* = 246 (M^+).

7-Chloro-1,2,3,4,4a,10a-hexahydrodibenzo[*b*,*e*][1,4]dioxine[15h] (9d)
White solid; mp 115–118 °C (Lit. 116–118 °C); R_f = 0.80 (hexanes–EtOAc, 95:5).

FT-IR (neat): 705, 720, 1060, 1275, 2865, 2942, 3052 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.52 (m, 4 H), 1.79–1.88 (m, 2 H), 2.18–2.26 (m, 2 H), 3.63–3.73 (m, 2 H), 6.76–6.79 (m, 2 H), 6.85–6.87 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 30.1, 30.2, 76.7, 117.3, 117.9, 121.3, 125.7, 142.8, 144.5.

MS (EI): *m*/*z* = 224 (M^+).

2,3,3a,9a-Tetrahydro-1*H*-benzo[*b*]cyclopenta[*e*][1,4]dioxine (9f)

White solid; mp 116 °C; R_f = 0.66 (hexanes–EtOAc, 95:5).

FT-IR (neat): 705, 750, 1254, 2880, 2974, 3047 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67–1.80 (m, 2 H), 1.87–1–97 (m, 2 H), 2.14–2.24 (m, 2 H), 3.92–4.01 (m, 2 H), 6.85–6.95 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0, 24.9, 78.5, 117.9, 121.8, 144.3.

HRMS: *m*/*z* [M + Na^+] calcd for $C_{11}H_{12}NaO_2$: 199.0735; found: 199.0738.

6-Phenyl-2,3,3a,9a-tetrahydro-1*H*-benzo[*b*]cyclopenta[*e*][1,4]dioxine (9g)

White solid; mp 132 °C; R_f = 0.62 (hexanes–EtOAc, 95:5).

FT-IR (neat): 700, 749, 1265, 2882, 2923, 2984, 3053 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70–1.83 (m, 2 H), 1.90–1.99 (m, 2 H), 2.18–2.27 (m, 2 H), 3.98–4.07 (m, 2 H), 7.0 (d, *J* = 8.4 Hz, 1 H), 7.14 (dd, *J* = 2.0, 8.4 Hz, 1 H), 7.20 (d, *J* = 2.4 Hz, 1 H), 7.29–7.36 (m, 1 H), 7.39–7.46 (m, 2 H), 7.54–7.59 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.0, 24.9, 29.5, 78.6, 78.6, 116.5, 118.2, 120.6, 126.9, 127.0, 128.8, 135.2, 140.6, 143.8, 144.4.

(*Z*)-5a,6,7,10,11,11a-Hexahydrobenzo[*b*]cycloocta[*e*][1,4]dioxine (9h)

Colorless oil; R_f = 0.83 (hexanes–EtOAc, 95:5).

FT-IR (neat): 744, 766, 1266, 2833, 2919, 3008, 3044 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.04 (m, 2 H), 2.21–2.31 (m, 2 H), 2.42–2.53 (m, 2 H), 2.60–2.72 (m, 2 H), 4.15–4.22 (m, 2 H), 5.59–5.63 (m, 2 H), 6.81–6.92 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 29.7, 76.6, 116.7, 121.1, 128.6, 144.1.

HRMS: *m*/*z* [M + H^+] calcd for $C_{14}H_{17}O_2$: 217.1229; found: 217.1228.

2-Phenyl-2,3-dihydro-1,4-benzodioxine[15h] (9i)

White solid; mp 55–57 °C (Lit. 54–56 °C); R_f = 0.68 (hexanes–EtOAc, 95:5).

FT-IR (neat): 699, 746, 1261, 2866, 2938, 3049 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (dd, *J* = 9.2, 11.2 Hz, 1 H), 4.33 (dd, *J* = 2.4, 11.4 Hz, 1 H), 5.11 (dd, *J* = 2.0, 8.8 Hz, 1 H), 6.85–7.01 (m, 4 H), 7.33–7.44 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.5, 75.2, 117.2, 117.7, 121.1, 121.7, 126.6, 127.0, 128.9, 136.6, 143.2, 144.0.

HRMS: *m*/*z* [M + H_2O] calcd for $C_{14}H_{14}O_3$: 230.0943; found: 230.0949.

2-Benzyl-2,3-dihydro-1,4-benzodioxine (9j)

Colorless oil; R_f = 0.62 (hexanes–EtOAc, 95:5).

FT-IR (neat): 700, 725, 1263, 2929, 3027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93 (dd, *J* = 7.2, 14.0 Hz, 1 H), 3.15 (dd, *J* = 6.4, 14.0 Hz, 1 H), 3.95 (dd, *J* = 6.8, 11.2 Hz, 1 H), 4.21 (dd, *J* = 2.4, 11.4 Hz, 1 H), 4.40 (dq, *J* = 2.4, 13.8 Hz, 1 H), 6.87–6.98 (m, 4 H), 7.28–7.42 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.6, 67.0, 73.8, 117.2, 117.5, 121.4, 121.7, 126.9, 128.7, 129.5, 136.5, 143.3, 143.4.

Total Synthesis of Isovanillyl Sweeteners

3-Acetyl-4-methoxybenzaldehyde (21)

To a stirred soln of isovanillin (**17**, 5g, 32.8 mmol, 1 equiv), DMAP (few crystals), and pyridine (5.3 mL, 65.6 mmol, 2 equiv) in CH_2Cl_2 at 0 °C was added AcCl (2.35 mL, 32.8 mmol, 1 equiv) dropwise and the resulting mixture was slowly warmed up to r.t. and stirred for 3 h. The mixture was then washed with 2 M HCl and the organic layer was separated, dried (anhyd Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc,) afford **21** (6.1 g, 96%) as a white solid; R_f = 0.56 (hexanes–EtOAc, 70:30).

FT-IR (neat): 781, 873, 1264, 1683, 1762, 2859, 3013, 3066 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 3.85 (s, 3 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 7.52 (d, *J* = 2.0 Hz, 1 H), 7.69 (dd, *J* = 2.0, 8.4 Hz, 1 H), 9.79 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 56.3, 112.1, 123.5, 130.1, 130.3, 140.3, 156.5, 168.8, 190.2.

HRMS: *m*/*z* [M + H^+] calcd for $C_{10}H_{11}O_4$: 195.0657; found: 195.0652.

3-Acetyl-4-methoxystyrene (18)

NaH (721.3 mg, 7 equiv) was added to a stirred suspension of $MePh_3P^+Br^-$ (2.76 g, 3 equiv) in benzene (6 mL). The suspension was stirred at r.t. for 12 h. To the yellow-colored suspension, **21** (500 mg, 2.57 mmol, 1 equiv) was added and the resulting mixture was stirred for 2 h. The crude product was extracted with EtOAc and the organic layer was separated, dried (anhyd Na_2SO_4), and the solvent removed under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes–EtOAc,) to afford **18** (320 mg, 65%) as a pale-yellow solid; R_f = 0.59 (hexanes–EtOAc, 90:10).

FT-IR (neat): 788, 817, 1270, 1762, 2850, 2926 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.83 (s, 3 H), 5.16 (d, *J* = 10.8 Hz, 1 H), 5.59 (d, *J* = 17.6 Hz, 1 H), 6.62 (dd, *J* = 10.8, 17.6 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 7.13 (s, 1 H), 7.22 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 56.1, 112.3, 112.8, 120.3, 125.2, 131.1, 135.7, 139.9, 150.9, 169.2.

HRMS: *m*/*z* [M + H^+] calcd for $C_{11}H_{13}O_3$: 193.0865; found: 193.0476.

2-Methoxy-5-(oxiran-2-yl)phenyl Acetate (19)

To a stirred suspension of alkene **18** (500 mg, 2.63 mmol, 1.0 equiv), and $NaHCO_3$ (2.5 g, 31.6 mmol, 12.0 equiv) in acetone (20 mL) at 0 °C was added a soln of Oxone (5 g, 8.42 mmol, 3.2 equiv) in H_2O (20 mL) dropwise over a period of 30 min. The resulting mixture was stirred at r.t. for 30 min and the mixture was extracted with Et_2O. The organic layer was separated, dried (anhyd Na_2SO_4), and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane–EtOAc) to afford **19** (368 mg, 68%) as a pale-yellow oil; R_f = 0.46 (hexanes–EtOAc, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 2.76 (dd, *J* = 2.8, 5.4 Hz, 1 H), 3.10 (dd, *J* = 4.0, 5.2 Hz, 1 H), 3.80 (dd, *J* = 2.8, 3.8 Hz, 1 H), 3.82 (s, 3 H), 6.91–6.96 (m, 2 H), 7.13 (dd, *J* = 2.0, 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 51.2, 51.9, 56.1, 112.5, 120.1, 124.3, 130.3, 140.0, 151.2, 169.1.

HRMS: *m*/*z* [M + H^+] calcd for $C_{11}H_{13}O_4$: 209.0814; found: 209.0816.

5-[1-Hydroxy-2-(2-iodophenoxy)ethyl]-2-methoxyphenol (22a)
Following the typical procedure for **8a** gave **22a** as a dark-brown oil; yield: 55%; R_f = 0.42 (hexanes–EtOAc, 65:35).

FT-IR (neat): 705, 750, 1111, 1267, 2844, 2922, 3271 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.77 (dd, *J* = 3.6, 12.2 Hz, 1 H), 3.85 (s, 3 H), 3.96 (dd, *J* = 8.4, 12.0 Hz, 1 H), 5.17 (dd, *J* = 3.2, 8.4 Hz, 1 H), 6.61–6.70 (m, 2 H), 6.79–6.90 (m, 2 H), 6.96 (d, *J* = 1.6 Hz, 1 H), 7.06–7.14 (m, 1 H), 7.71–7.77 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 67.6, 82.7, 87.5, 111.0, 112.7, 114.4, 118.1, 123.1, 129.5, 130.4, 139.3, 146.1, 146.7, 156.3.

HRMS: *m/z* [M + Na^+] calcd for $C_{15}H_{15}INaO_4$: 408.9991; found: 408.9995.

5-[1-Hydroxy-2-(2-iodophenylthio)ethyl]-2-methoxyphenol (22b)
Following the typical procedure for **8a** gave **22b** as a brown oil; yield: 60%; R_f = 0.35 (hexanes–EtOAc, 70:30).

FT-IR (neat): 650, 1168, 1268, 2928, 3392 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.11 (dd, *J* = 9.2, 13.6 Hz, 1 H), 3.27 (dd, *J* = 4.0, 13.8 Hz, 1 H), 3.87 (s, 3 H), 4.69 (dd, *J* = 3.6, 9.2 Hz, 1 H), 5.73 (br s, 1 H), 6.79–6.98 (m, 4 H), 7.28–7.40 (m, 2 H), 7.84 (dd, *J* = 1.2, 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.3, 56.1, 71.5, 101.6, 110.7, 112.3, 117.7, 127.8, 128.9, 129.2, 135.5, 139.9, 140.4, 145.8, 146.5.

HRMS: *m/z* [M + Na^+] calcd for $C_{15}H_{15}INaO_3S$: 424.9763; found: 424.9759.

5-(2,3-Dihydro-1,4-benzodioxin-2-yl)-2-methoxyphenol[19] (7a)
Phenol **22a** (193 mg, 0.50 mmol), BINOL (**L6**, 28.6 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and Cs_2CO_3 (325 mg, 1.0 mmol) were added to a sealed tube and equipped with screw cap. The sealed tube was evacuated and backfilled with N_2. MeCN (3 mL) was added to the mixture at r.t. and the mixture was heated at 110 °C for 36 h. After complete disappearance of **22a** (TLC monitoring), the mixture was allowed to cool to r.t. and the solvent was removed by evaporation. The crude residue was purified by column chromatography (silica gel, EtOAc–hexanes) to afford **7a** (86.4 mg, 67%) as a white solid; mp 96–98 °C (Lit. 98–99 °C); R_f = 0.56 (CH_2Cl_2–EtOAc, 80:20).

FT-IR (neat): 750, 803, 1246, 1267, 2930, 3511 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 3.89–3.98 (m, 1 H), 4.24 (dd, *J* = 1.6, 11.6 Hz, 1 H), 4.95 (d, *J* = 8.8 Hz, 1 H), 5.63 (br s, 1 H), 6.77–6.94 (m, 7 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.2, 69.4, 74.9, 110.9, 113.0, 117.2, 117.7, 118.5, 121.6, 121.7, 129.8, 143.2, 144.1, 146.1, 147.0.

HRMS: *m/z* [M + H^+] calcd for $C_{15}H_{15}O_4$: 259.0970; found: 259.0950.

5-(2,3-Dihydro-1,4-benzooxathiin-2-yl)-2-methoxyphenol[20] (7b)
Thiophenol **22b** (201 mg, 0.50 mmol), BINOL (**L6**, 28.6 mg, 0.1 mmol), CuI (19 mg, 0.1 mmol), and Cs_2CO_3 (325 mg, 1.0 mmol) were added to a sealed tube and equipped with screw cap. The sealed tube was evacuated and backfilled with N_2. MeCN (3 mL) was added to the mixture at r.t. and the mixture was heated at 110 °C for 36 h. After complete disappearance of **22b** (TLC monitoring), the mixture was allowed to cool to r.t. and the solvent was removed by evaporation. The crude residue was purified by column chromatography (silica gel, EtOAc–hexanes) to afford **7b** (86.3 mg, 63%) as a yellow solid; mp 127–129 °C (Lit. 128 °C); R_f = 0.43 (CH_2Cl_2–EtOAc, 80:20).

FT-IR (neat): 750, 760, 1266, 1275, 2987 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.05 (dd, *J* = 1.6, 13.2 Hz, 1 H), 3.27 (dd, *J* = 9.6, 13.2 Hz, 1 H), 3.91 (s, 3 H), 5.06–5.13 (m, 1 H), 5.70 (br s, 1 H), 6.84–6.95 (m, 4 H), 6.97–7.05 (m, 2 H), 7.08–7.14 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.9, 56.2, 76.4, 110.8, 112.5, 117.3, 118.0, 118.9, 121.7, 125.8, 127.3, 133.7, 146.0, 146.8, 152.5.

HRMS: *m/z* [M + H^+] calcd for $C_{15}H_{15}O_3S$: 275.0742; found: 275.0766.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. Included are the ^1H and ^{13}C NMR spectra data for all the compounds.

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