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Competition of substituents for *ortho* direction of metalation of veratric acid

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ABSTRACT

LTMP (5 equiv) metalates randomly veratric acid (**1**). Under external quench conditions, the thermodynamically more stable lithium 2-lithio-3,4-dimethoxybenzoate (**2**) reacts with a variety of electrophiles to give versatile building units that are not easily accessible by conventional means. Under in situ quench conditions (LTMP/TMSCl), a reversal of regioselectivity is observed and 6-trimethylsilyl-3,4-dimethoxybenzoic acid (**10**) is formed predominantly.

1. Introduction

It is well known that certain substituents containing heteroatoms are able to promote the lithiation of an aromatic ring at the *ortho* position (*ortho*-lithiation) by hydrogen–metal exchange with an alkyllithium reagent.[1,2] The effect of the heteroatom has been explained in terms both of increased intrinsic acidity of the *ortho* proton and of coordination of the metalating agent with consequent enhancement of its ability to abstract the *ortho* proton.[2,3]

The directed metalation group CO_2H increases the discrimination between *ortho* positions and favors metalation over nucleophilic addition reactions to the aromatic nucleus.[4] We have recently described its synthetic utility by demonstrating a series of regioselective reactions derived from the competition of halobenzoic acids,[5] anisic acids,[6] and biphenyl carboxylic acids[7] with organolithiums and superbases.

Herein we record details of our investigations on the metalation of veratric acid (**1**). As this article will demonstrate, the 'in situ quench protocol' provides a powerful alternative to the stepwise reaction. We describe methodological aspects related to the preparation of contiguously 2-substituted-3,4-dimethoxybenzoic acids, which have found wide uses in many areas of pesticidal, pharmaceutical, and materials chemistry as versatile intermediates. For instance, 3,4-dimethoxy-2-methylbenzoic acid is a key intermediate for the synthesis of HIV protease inhibitors,[8] for the preparation of analogs of quercetin[9] and gossypol.[10,11] 2-Chloro-3,4-dimethoxybenzoic acid is a core building unit for the synthesis of, inter alia, urea inhibitors of protein kinases such as the mitogen-activated protein kinases,[12] analogs of lamellarin,[13] and arylpiperazine-benzoylamide derivatives of pharmaceutical interest.[14] In the prior art, 2-substituted-3,4-dimethoxybenzoic acids were prepared by demanding classical and poorly regioselective multisteps sequences in low overall yield.[15] *ortho*-(Methoxy)aryloxazolines react with organolithium or Grignard reagents to give 2-substituted derivatives resulting from the nucleophilic methoxy displacement,[16] whereas *meta*-(methoxy)aryloxazolines are deprotonated at the C-2 position by *n*-BuLi.[17] Nevertheless these transformations require laborious protection and deprotection steps to restore the carboxylic acid moiety.

2. Results and discussion

General conditions were chosen on the basis of preliminary experiments with different bases (Scheme 1 and Table 1). Veratric acid (**1**) did not undergo any detectable metalation when LDA was used in excess (5 equiv) in THF at 0 °C (entry 1). The reaction was sluggish even at 66 °C (entry 2). 3,4-Dimethoxy-2-methylbenzoic acid (**5**) was prepared in only 9% yield after addition of iodomethane at 40 °C. So we turned to the more basic lithium 2,2,6,6-tetramethylpiperidide (LTMP). The pK_a values for diisopropylamine and tetramethylpiperidine in THF are, respectively, 35.7 and 37.3.[18] A yield of 44% was obtained with 2.2 equiv of the latter base (entry 3).

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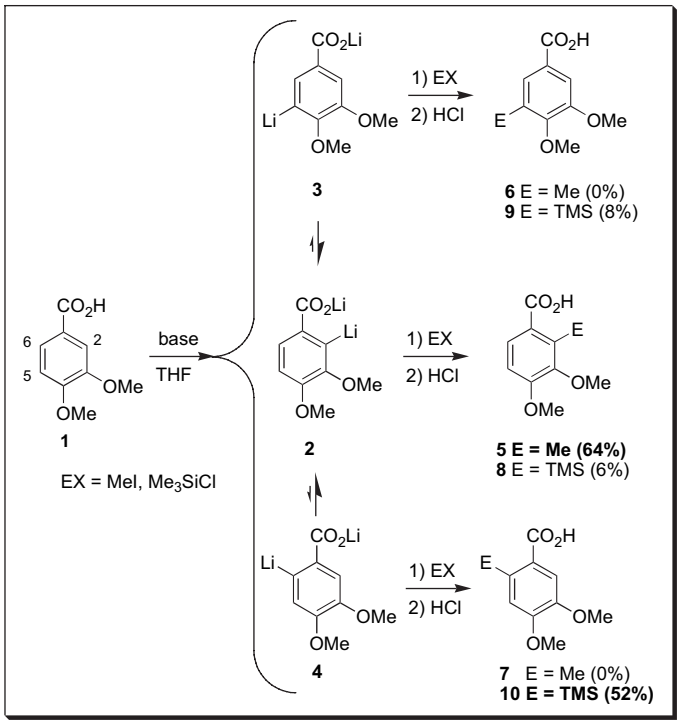
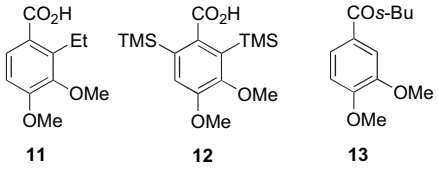




Scheme 1. Metalation of veratric acid (**1**).

Optimization of the reaction conditions for the formation of **5** showed that the best yield thereof (64%) was obtained when metalation was carried out with 4 equiv of LTMP in THF at 0 °C, after in situ formation of the lithium salt of **1** with 1 equiv of *n*-BuLi at −78 °C, followed by addition of MeI and gentle warming at 40 °C (external quench, entry 4). Since 2-ethyl-3,4-dimethoxybenzoic acid (**11**) that arises from the lateral metalation of **5** was also formed under these conditions,[19] the yield of aromatic metalation is the combination of the yields of **5** and **11** (91%). The yield of **5** did not improve when **2** was added slowly to MeI in THF at 0 °C (reverse addition).[20]

The in situ quench (ISQ) protocol,[21] in which the acid **1** was added to a solution containing LTMP (3 equiv) and TMSCl (3 equiv) at −78 °C gave a mixture of 2-trimethylsilyl-3,4-dimethoxybenzoic acid (**8**) and 6-trimethylsilyl-3,4-dimethoxybenzoic acid (**10**) (entry 5). With 5 equiv of LTMP, **10** was formed predominantly (**8**/**9**/**10**,

Table 1
Metalation of veratric acid (**1**) with strong bases

Entry	Conditions[b,c]	Yield[a] (%)			
		C-2	C-5	C-6	Others
1	(1) LDA (5 equiv), 0 °C (2) MeI, 0 °C→40 °C	0	0	0	—
2	(1) LDA (5 equiv), 66 °C (2) MeI, 40 °C	9 [**5**]	0	0	—
3	(1) LTMP (2.2 equiv), 0 °C (2) MeI, 0 °C→40 °C	44 [**5**]	0	0	<3 [**11**]
4	(1) *n*-BuLi (1 equiv), −78 °C (2) LTMP (4 equiv), 0 °C (3) MeI, 0 °C→40 °C	64 (40* [**5**])	0	0	27 [**11**]
5	LTMP (3 equiv), TMSCl (3 equiv) (ISQ), −78 °C→rt	15 [**8**]	0	15 [**10**]	<3 [**12**]
6	LTMP (5 equiv), TMSCl (5 equiv) (ISQ), −78 °C→rt	6 [**8**]	8 [**9**]	52 (20* [**10**])	34 (10* [**12**])
7	(1) LTMP (5 equiv), 0 °C (2) TMSCl (5 equiv), 0 °C→rt	35 (15* [**8**])	0	3 [**10**]	—
8	(1) *s*-BuLi/TMEDA (5 equiv), −78 °C→−30 °C (2) MeI, −30 °C→rt	21 [**5**]	6 [**6**]	35 [**7**]	22 [**13**]
9	(1) *s*-BuLi/TMEDA (2.2 equiv), −30 °C (2) MeI, −30 °C→rt	0	0	0	22 [**13**]
10	(1) *n*-BuLi/*t*-BuOK (4 equiv), −78 °C→−50 °C (2) MeI, −78 °C→rt	22 [**5**]	51 [**6**]	17 [**7**]	—

[a] Yields and product ratios were determined by ^{1}H NMR after acidification of the crude reaction mixture and extraction with ether. Products **8**, **10**–**13** were isolated by chromatography (cyclohexane/ethylacetate 7:3). Isolated yields are followed by an asterisk (*).

[b] Reactions were carried out in THF. The base was allowed to react with **1** for 2 h. External quench (EQ) technique except ortherwise noted. In situ quench (ISQ): the acid **1** was added to a solution of LTMP and TMSCl in THF at −78 °C. Hydrolysis (2 M HCl) was carried out at rt.

[c] Acids **5**–**7** are known in the literature. (**5**): see Ref. 28; (**6**): Borchardt, R. T.; Bhatia, P. *J. Med. Chem.* **1982**, *25*, 263–271; (**7**): Wu, T-C.; Rieke, R. D. *J. Org. Chem.* **1988**, *53*, 2378–2381.

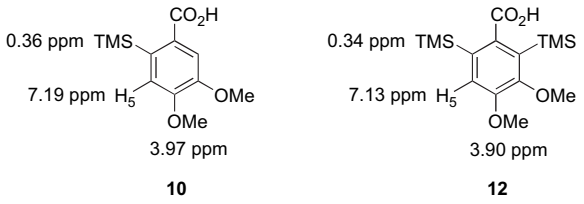


Figure 1.

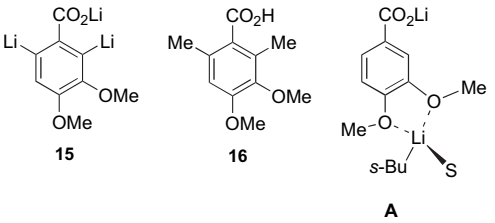
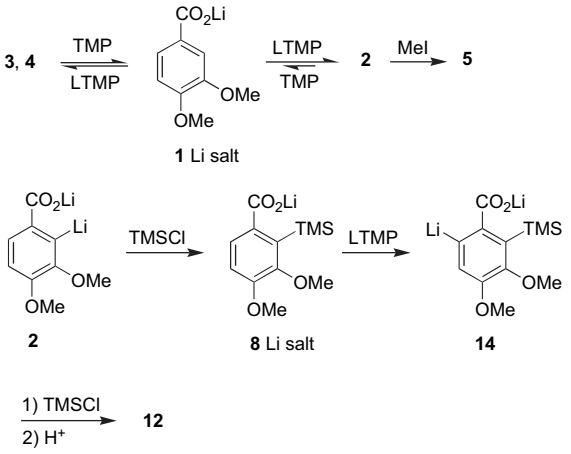


Figure 2.

6:8:52 ratio, entry 6), along with an appreciable amount of the disilylated product **12** (34%). A reversal of regioselectivity was observed when TMSCl was added to the preformed dianion (**8**/**9**/**10**, 35:0:3 ratio, entry 7). Proof for the location of the TMS groups of **10** and **12** was gathered by the NOESY technique (Fig. 1). For **10**, the hydrogen H-5 situated at 7.19 ppm shows clear interactions with the methoxy group at 3.97 ppm as well as with the TMS group at 0.36 ppm. Therefore the TMS group of **10** is located in the position *ortho* to the carboxylate (C-6). The carboxylate of **12** is flanked by two TMS groups since the hydrogen H-5 (7.13 ppm) shows NOESY interactions with the methoxy group at 3.90 ppm and the TMS group at 0.34 ppm.

These results can be rationalized as follows. The fact that the deprotonation of **1** by LTMP/TMSCl is not regioselective under ISQ conditions (entries 5 and 6) strongly suggests that the three dianions **2**–**4** are formed. Under similar conditions, we have showed previously that reaction of *meta*-anisic acid provides a 75% yield of 2-trimethylsilyl-3-methoxybenzoic acid.[6a]

5-Lithio- and 6-lithio-3,4-dimethoxybenzoates (**3** and **4**), by a protonation/deprotonation sequence involving 2,2,6,6-tetramethylpiperidine (TMP)/LTMP, isomerize to the thermodynamically more stable—less basic—2-lithio isomer **2** under standard external quench conditions (entries 2–4, Scheme 2). The dianion **2** remains indefinitely stable even in refluxing THF (+66 °C). After MeI trapping, 3,4-dimethoxy-2-methylbenzoic acid (**5**) is formed as the sole product.



Scheme 2. Mechanism of formation of **12** under ISQ conditions.

Under ISQ conditions, the reaction of **2**–**4** with TMSCl is competitive in rate with the isomerization of **3** and **4** leading to **2**. The remaining TMSCl does not destroy the excess of LTMP, which can then deprotonate **8** further to give **14** whose reaction with TMSCl affords **12**.

The intermediacy of lithium 2,5-dilithiobenzoate **15** can be ruled out since such a species by reaction with MeI would be expected to give **16**, which was not isolated (Fig. 2). The isomerization **3**,**4**→**2** was not observed in the absence of a proton source. Treatment of **1** with the 1:1 complex *s*-BuLi/TMEDA (5 equiv) in THF at −78 °C followed by addition of MeI at −30 °C gave a mixture of **5**–**7** (21:6:35, entry 8). Veratric acid (**1**) was not metalated at all upon treatment with 2.2 equiv of *s*-BuLi/TMEDA (entry 9) presumably because the p-electrons of the methoxy groups coordinate strongly with the second equivalent of base, leading to a complex of the type **A**.[22] The undesired ketone **13** resulting from the nucleophilic addition of *s*-BuLi to the carboxylate was also formed.[23]

Superbases preferentially attack the inductively activated aromatic position next to the most electronegative heteroatom and/or the most acidic position available.[24] Addition of **1** to 4 equiv of preformed LICKOR made of equimolecular amounts of *n*-butyllithium and potassium *tert*-butoxide,[25] followed by quench with iodomethane (0 °C→40 °C) provided the acids **5**, **6**, and **7** (22:51:17 ratio, entry 10). Metalation of **1** with 4 equiv of LICKOR at 60 °C in benzene failed.[7a,26]

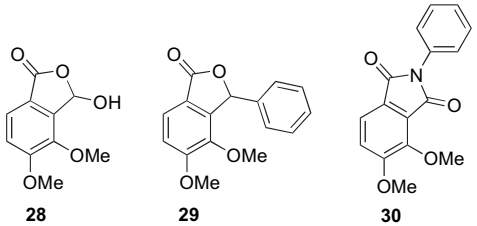
According to the optimized conditions found at entry 4 (Table 1), the lithio benzoate **2** also reacted, to give the expected *ortho*-substituted products, with sundry other electrophilic reagents, which included deuterium oxide, iodoethane, hexachloroethane, 1,2-dibromotetrachloroethane, iodine, dimethyl disulfide, carbon dioxide, DMF, benzaldehyde, phenylisocyanate, and dioxygen (Table 2). The substituted veratric acids thus obtained are versatile materials for organic synthesis (vide supra).[8–14] Although yields are only fair, they are usable since no protection and deprotection of the reactive carboxylic acid group are needed.[27]

Quenching with DMF or benzaldehyde afforded the primary products **24** and **25**, which cyclized spontaneously to give phthalide **28** and lactone **29**, respectively. *N*-Phenylphthalimide (**30**) was

Table 2
Synthesis of 2-substituted-3,4-dimethoxybenzoic acids

EX	E	Product[a] (%)	Mp (°C)	Lit. mp (°C)
D_2O	D	50 [**18**]	—	—
MeI	Me	40 [**5**]	180–182	184[28]
EtI	Et	10 [**11**]	152–154	152–154[29]
C_2Cl_6	Cl	40 [**19**]	201.5–202	200–202[30]
$C_2Br_2Cl_4$	Br	47 [**20**]	204–205	206–208[31]
I_2	I	55 [**21**]	204.5–205	205–206[32]
Me_2S_2	MeS	45 [**22**]	88.5–90.5	—
CO_2	CO_2H	68 [**23**]	170–171	177[33]
DMF	CHO	34 [**24**][b]	118–119	—
PhCHO	Ph(CHOH)	40 [**25**][c]	94–94.5	92.5–93[34]
PhNCO	PhNHCO	35 [**26**][d]	161–163	162[35]
O_2	OH	24 [**27**]	—	170–172[36]

[a] Isolated yields.
[b] Product cyclized into hydroxyphthalide **28**.
[c] Product cyclized into lactone **29**.
[d] Product cyclized into phthalimide **30**.



isolated in 35% yield by quench with phenylisocyanate. The one-pot lithiation/oxygenation sequence (LTMP then O_2) gave a moderate yield of the regiospecifically monohydroxylated product **27**.

3. Conclusion

In summary, the three aromatic hydrogens of veratric acid (**1**) have similar kinetic acidities. Due to the cooperative effect of the 1,3-interrelated *ortho*-directors CO_2Li and 3-MeO in promoting metalation at their common site, the hydrogen H-2 is thermodynamically more acidic. *ortho*-Functionalization of **1** and presumably derivatives thereof, via the corresponding dilithio species **2** provides a rapid, facile, and practical means of synthesis of *ortho*-substituted benzoic acids and compounds derived therefrom, which are versatile starting material for organic synthesis. Under in situ quench conditions, a reversal of regioselectivity is observed and the anion **4** resulting from the metalation at C-6 is trapped by TMSCl preferentially. Hence, the CO_2H group permits a remarkable degree of control of the regioselectivity of metalation between nonequivalent *ortho* centers.

4. Experimental section

4.1. General

For standard working practice, see Ref. 37. Reactions were carried out under argon in heat gun-dried glassware. Tetrahydrofuran was dried from sodium benzophenone ketyl. NMR spectra were recorded on a 200- or 400-MHz spectrometer. ^{13}C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in $CDCl_3$, chemical shifts were recorded relative to the internal TMS (tetramethylsilane) reference signal. For DMSO-d_6, chemical shifts are given relative to the solvent signal. IR spectra were recorded on a FTIR spectrophotometer. All melting points are uncorrected. Commercial reagents were used without further purification. Chromatography was performed with silica gel (40–60 μm). *n*-BuLi (1.6 M in hexanes) and *s*-BuLi (1.3 M in cyclohexane/hexanes) were titrated periodically against 2,5-dimethoxybenzyl alcohol. *N*,*N*,*N*′,*N*′-Tetramethyl-1,2-ethylenediamine (TMEDA) was distilled from CaH_2. Potassium *tert*-butylate (*t*-BuOK) was sublimated.

4.2. 2-Substituted 3,4-dimethoxybenzoic acids (5, 8, 10–12, 18–23, 27–30)

*4.2.1. In situ quench technique. 3,4-Dimethoxy-6-(trimethylsilyl)benzoic acid (**10**) and 3,4-dimethoxy-2,6-(trimethylsilyl)benzoic acid (**12**) (entry 6, Table 1)*

To a solution of LTMP (15 mmol) in THF (20 mL) at −78 °C were added successively chlorotrimethylsilane (1.94 mL, 15 mmol) and 3,4-dimethoxybenzoic acid (**1**) (0.552 g, 3 mmol) in THF (10 mL). After 1 h at −78 °C, the mixture was warmed gradually to 0 °C for 2 h, and then allowed to warm to ambient temperature. Water (30 mL) and aqueous (2 M) NaOH were added successively (pH 10), the aqueous layer was washed with ether (2×20 mL), acidified with aqueous 2 M HCl (pH 1–2), and extracted with ether (3×30 mL). The organic layer was dried over $MgSO_4$, filtrated, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (cyclohexane/ethylacetate 9:1→8:2) to give **10** (152 mg, 20%) as a white solid (mp 166.5–167.0 °C). R_f=0.25 (cyclohexane/ethylacetate 7:3). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.74 (s, 1H), 7.19 (s, 1H), 3.97 (s, 6H), 0.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5, 152.0, 148.8, 137.7, 126.7, 117.7, 116.0, 55.9, 55.8, 0.5. IR (neat): 2939, 2841, 1682 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4Si$: C, 56.66; H, 7.13. Found: C, 56.64; H, 7.16. HRMS *m*/*z* calcd for $C_{12}H_{18}O_4Si$ ($[M+H]^+$): 255.1053, found: 255.1056. Proof for the location of the TMS group of **10** was gathered by the NOESY technique (vide supra). In another chromatographic fraction, the disilylated product **12** was also isolated (98 mg, 10%). Yellow solid (mp 188.0–190.0 °C). R_f=0.43 (cyclohexane/ethylacetate 8:2). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.13 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 0.36 (s, 9H), 0.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.2, 154.8, 152.3, 136.4, 134.8, 132.4, 119.3, 60.7, 55.4, 1.52, 0.30. IR (neat): 2923, 2851, 1686, 1560 cm^{-1}. HRMS *m*/*z* calcd for $C_{15}H_{26}O_4Si_2$ ($[M+H]^+$): 327.1448, found: 327.1447. The regiochemistry of **12** was also confirmed by NOESY spectrum.

*4.2.2. External quench technique. 3,4-Dimethoxy-2-(trimethylsilyl)benzoic acid (**8**) (entry 7, Table 1)*

At 0 °C, LTMP (15 mmol) in dry THF (20 mL) was added dropwise to a stirred solution of **1** (0.552 g, 3 mmol) in THF (10 mL). The solution was stirred for 2 h at 0 °C and chlorotrimethylsilane was added (1.94 mL, 15 mmol). After 2 h at this temperature, the mixture was allowed to warm to ambient temperature and water (30 mL) was added. Aqueous 2 M NaOH was added (pH 10), the aqueous layer was washed with ether (2×20 mL), acidified with aqueous 2 M HCl (pH 1–2), and extracted with ether (3×30 mL). The organic layer was dried over $MgSO_4$, filtrated, and concentrated in vacuo to furnish the crude silylated benzoic acid, which was purified by chromatography (cyclohexane/ethylacetate 9:1) to give **8** (114 mg, 15%) as a white solid (mp 141.0–141.5 °C). R_f=0.35 (cyclohexane/ethylacetate 7:3). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, 1H, *J*=8.4 Hz), 6.93 (d, 1H, *J*=8.5 Hz), 3.91 (s, 3H), 3.82 (s, 3H), 0.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.8, 155.6, 154.8, 135.3, 129.2, 127.5, 111.8, 61.2, 55.6, 2.0. IR (neat): 2939, 1689, 1577 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_4Si$: C, 56.66; H, 7.13. Found: C, 56.54; H, 7.12. HRMS *m*/*z* calcd for $C_{12}H_{19}O_4Si$ ($[M+H]^+$): 255.1053, found: 255.1084.

*4.2.3. General procedure for the preparation of 2-substitued 3,4-dimethoxybenzoic acids (**5**, **11**, **18**–**23**, and **28**–**30**) (see also Table 2)*

To a stirred solution of lithium 3,4-dimethoxybenzoate [prepared by addition of 1 equiv of *n*-BuLi to veratric acid **1** (0.552 g, 3 mmol) at −78 °C] in dry THF (15 mL) at 0 °C, was added dropwise LTMP (12 mmol) in THF (20 mL). After 2 h stirring at this temperature, the solution was quenched with the electrophile (5 equiv). Stirring was maintained for 1 h, the solution was allowed to warm to ambient temperature (1 h), and then heated to 40–66 °C (1 h). Water (30 mL) was added, the aqueous phase was washed with ether (2×20 mL), acidified to pH 1–2 (2 M HCl), and extracted with ether (3×30 mL). The organic layer was dried over $MgSO_4$, filtrated, and concentrated in vacuo to give the crude benzoic acids (**5**, **11**, **18**–**23**, and **28**–**30**), which were chromatographed on silica gel or recrystallized.

*4.2.3.1. 2-Deuterio-3,4-dimethoxybenzoic acid (**18**).* See general procedure. The solution was quenched with deuterium oxide (0.3 mL, 15 mmol). Standard workup afforded **18** (50% crude yield). ^1H NMR (200 MHz, $CDCl_3$) δ: 7.79 (d, 1H, *J*=8.4 Hz), 6.93 (d, 1H, *J*=8.5 Hz), 3.96 (s, 3H), 3.96 (s, 3H).

*4.2.3.2. 3,4-Dimethoxy-2-methylbenzoic acid (**5**).* See general procedure. The solution was quenched with iodomethane (0.94 mL, 15 mmol). Standard workup followed by fractional crystallization (ethanol 95%) afforded **5** (235 mg, 40%) as a white solid (mp 180–182 °C, lit.[28] 184 °C). ^1H NMR (200 MHz, $CDCl_3$) δ: 7.90 (d, 1H, *J*=8.8 Hz), 6.82 (d, 1H, *J*=8.8 Hz), 3.93 (s, 3H), 3.79 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.8, 156.7, 147.5, 136.1, 128.8, 121.6, 108.7, 60.4, 55.8, 13.4. IR (neat): 2926, 2641, 1660 cm^{-1}. HRMS *m*/*z* calcd for $C_{10}H_{16}NO_4$ ($[M+NH_4]^+$): 214.1082, found: 214.1079.

*4.2.3.3. 3,4-Dimethoxy-2-ethylbenzoic acid (**11**).* See general procedure. The mixture was quenched with iodoethane (1.21 mL,

15 mmol). Standard workup followed by fractional crystallization (ethanol) afforded **11** (63 mg, 10%) as a yellow solid (mp 152–154 °C, lit.[29] 152–154 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, 1H, J=8.8 Hz), 6.82 (d, 1H, J=8.8 Hz), 3.93 (s, 3H), 3.84 (s, 3H), 3.11 (q, 2H, J=7.6, 7.3 Hz), 1.22 (t, 3H, J=7.6, 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.6, 156.6, 147.2, 142.2, 129.0, 126.7, 121.0, 108.9, 60.9, 55.7, 15.6, 12.6. IR (neat): 2929, 1660, 1590 cm^{-1}.

*4.2.3.4. 2-Chloro-3,4-dimethoxybenzoic acid (**19**).* See general procedure. The solution was quenched with hexachloroethane (3.55 g, 15 mmol). Standard workup followed by fractional crystallization (acetic acid) afforded **19** (260 mg, 40%) as a white solid (mp 201.5–202 °C, lit.[30] 200–202 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, 1H, J=8.8 Hz), 6.89 (d, 1H, J=9.0 Hz), 3.95 (s, 3H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.1, 155.9, 145.2, 127.2, 127.1, 123.3, 110.7, 60.0, 56.2. IR (neat): 2932, 1686, 1585 cm^{-1}.

*4.2.3.5. 2-Bromo-3,4-dimethoxybenzoic acid (**20**).* See general procedure. The solution was quenched with dibromotetrachloroethane (4.89 g, 15 mmol). Standard workup followed by fractional crystallization (acetic acid) afforded **20** (268 mg, 47%) as a white solid (mp 204–205 °C, lit.[31] 206–208 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (d, 1H, J=8.8 Hz), 6.92 (d, 1H, J=8.8 Hz), 3.95 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 166.7, 155.5, 148.2, 127.1, 125.6, 116.8, 111.4, 59.8, 56.2. IR (neat): 2927, 2079, 1660 cm^{-1}. HRMS m/z calcd for $C_9H_{10}BrO_4$ ([M+H]$^+$): 262.9743, found: 262.9770.

*4.2.3.6. 2-Iodo-3,4-dimethoxybenzoic acid (**21**).* See general procedure. The solution was quenched with iodine (3.81 g, 15 mmol). Standard workup followed by fractional crystallization (acetic acid) afforded **21** (508 mg, 55%) as a white solid (mp 204.5–205 °C, lit.[32] 205–206 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.86 (d, 1H, J=8.6 Hz), 6.93 (d, 1H, J=8.8 Hz), 3.94 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (50 MHz, DMSO-d_6) δ: 167.5, 154.3, 148.7, 129.2, 127.0, 112.1, 94.1, 59.6, 56.1. IR (neat): 2923, 2118, 1660 cm^{-1}.

*4.2.3.7. 3,4-Dimethoxy-2-methylthiobenzoic acid (**22**).* See general procedure. The solution was quenched with dimethyl disulfide (1.33 mL, 15 mmol). Standard workup followed by chromatography (cyclohexane/ethylacetate 40:60, R_f=0.22) and fractional crystallization (cyclohexane/ethylacetate) afforded **22** (308 mg, 45%) as a red-brown solid (mp 88.5–90.5 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.03 (d, 1H, J=8.8 Hz), 6.98 (d, 1H, J=8.9 Hz), 3.95 (s, 3H), 3.91 (s, 3H), 2.50 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 169.5, 156.6, 150.3, 131.4, 128.9, 125.0, 111.4, 60.6, 56.0, 19.4.

*4.2.3.8. 3,4-Dimethoxybenzen-1,2-dioic acid (**23**).* See general procedure. The solution was quenched with dry ice. Standard workup followed by fractional crystallization (water) afforded **23** (461 mg, 68%) as a pale yellow solid (mp 170–171 °C, lit.[38] 177 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, 1H, J=8.8 Hz), 7.19 (d, 1H, J=8.8 Hz), 3.99 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 167.9, 166.3, 157.6, 146.4, 133.4, 128.2, 120.6, 113.0, 61.6, 56.5. IR (neat): 3452, 2939, 2117, 1758 cm^{-1}.

*4.2.3.9. 3-Hydroxy-4,5-dimethoxyisobenzofuran-1(3H)-one (**28**).* See general procedure. The solution was quenched with dimethylformamide (1.17 mL, 15 mmol). Standard workup followed by chromatography (cyclohexane/ethylacetate 50:50, R_f=0.22) afforded **28** (214 mg, 34%) as a white solid (mp 118–119 °C).[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, 1H, J=8.3 Hz), 7.07 (d, 1H, J=8.3 Hz), 6.72 (s, 1H), 4.03 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.8, 157.1, 144.4, 136.8, 121.3, 119.7, 114.7, 96.0, 60.8, 56.5. IR (neat): 2930, 2117, 1736 cm^{-1}.

*4.2.3.10. 4,5-Dimethoxy-3-phenylisobenzofuran-1(3H)-one (**29**).* See general procedure. The solution was quenched with benzaldehyde (1.54 mL, 15 mmol). Standard workup followed by chromatography (cyclohexane/ethylacetate 7:3) afforded **29** (324 mg, 40%) as a white solid (mp 94–94.5 °C, lit.[34] 92.5–93.0 °C). R_f=0.35 (cyclohexane/ethylacetate 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69 (d, 1H, J=8.3 Hz), 7.39–7.26 (m, 5H), 7.10 (d, 1H, J=8.3 Hz), 6.39 (s, 1H), 3.94 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 170.1, 158.6, 144.1, 143.4, 138.2, 129.9, 129.5, 128.3, 122.2, 119.6, 115.8, 81.2, 60.1, 56.9. IR (neat): 2939, 1760, 1609 cm^{-1}. HRMS m/z calcd for $C_{16}H_{15}O_4$: 271.0970 ([M+H]$^+$), found: 271.0957.

*4.2.3.11. 4,5-Dimethoxy-2-phenylisoindoline-1,3-dione (**30**).* See general procedure. The solution was quenched with phenylisocyanate (1.66 mL, 15 mmol). Standard workup followed by chromatography (ethylacetate, R_f=0.13) afforded **30** (297 mg, 35%) as a yellow solid (mp 161–163 °C, lit.[35] 162 °C). ^{1}H NMR (400 MHz, acetone-d_6) δ: 7.68 (d, 1H, J=8.7 Hz), 7.65 (d, 2H, J=8.7 Hz), 7.18 (dd, 2H, J=7.5, 7.6 Hz), 7.04 (d, 1H, J=8.7 Hz), 6.93 (t, 1H, J=7.4 Hz), 3.84 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ: 166.3, 165.3, 165.2, 157.5, 146.8, 140.8, 136.0, 129.4, 128.3, 123.9, 121.2, 120.3, 120.2, 112.8, 61.7, 56.5. IR (neat): 2985, 1684, 1591 cm^{-1}.

*4.2.3.12. 3,4-Dimethoxy-2-hydroxybenzoic acid (**27**).* See general procedure. The solution was quenched with oxygen. After being stirred for 1 h at 0 °C, the reaction mixture was allowed to warm to ambient temperature and then hydrolyzed. Standard workup afforded **27** (24% crude yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.72 (d, 1H, J=8.8 Hz), 6.54 (d, 1H, J=8.8 Hz), 3.94 (s, 3H), 3.90 (s, 3H).[40]

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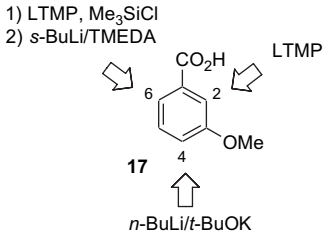

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