A New Application of the Pictet–Spengler Reaction to the Preparation of 4-Substituted 1*H*-2,3-Benzoxazines

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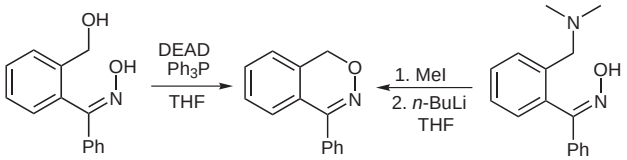
Abstract: Intramolecular coupling reaction of benzylic *O*-hydroxamates and aldehydes was investigated to afford a variety of 4-substituted 1*H*-2,3-benzoxazine ring systems in good to excellent yields. The reaction involved an intramolecular C–C bond formation between an *N*-acyl- or *N*-sulfonyl-oxoiminium ion with the aryl ring. Under the studied conditions, electron-donating groups in the aryl ring are essential for the desired coupling reactions.

Key words: 1*H*-2,3-benzoxazine, Pictet–Spengler reaction, oxoiminium ion, hydroxamate, aldehyde

The Pictet–Spengler reaction is an acid-catalyzed intramolecular cyclization of the intermediate imine of 2-arylethylamine formed by condensation with a carbonyl compound.[1] It has been widely used in the formation of tetrahydroisoquinolines and tetrahydrocarbolines, which are present in numerous natural products and synthetic medical compounds possessing biological activities.[2] This reaction has found wide application in the following three amine prototypes: dopamine/tyramine,[3] tryptophan/tryptamine,[3] histidine/histamine.[4] However, to the best of our knowledge, the Pictet–Spengler cyclization has never been applied to the related benzyloxyamine derivatives **1** (Scheme 1). This prompted us to explore the use of hydroxamates **1** as possible substrates for the Pictet–Spengler reaction to give N–O fused 1*H*-2,3-benzoxazines **2**. Additionally, the heterocycle itself may be a useful scaffold for the development of drug leads, among which some compounds possess CNS depressant activity[5] and herbicidal activity.[6]

Traditionally, 1*H*-2,3-benzoxazines **2** can be made from **5**, which have been prepared from **3** and **4** by the Mitsunobu reaction[6,7] and base-catalyzed cyclization[5,8] (Scheme 2). However, these methods require 1,2-disubstituted substrates, and the geometry of the oxime is restricted to the *syn*-isomer. Additionally, these reaction conditions are carefully chosen to avoid the formation of nitrone by intramolecular N-alkylation.[9] Herein a convenient method to construct **2** from **1** by Lewis acid induced Pictet–Spengler reaction[10] is described (Scheme 1). This strategy allows 4-substituted 1*H*-2,3-benzoxazines to be synthesized from hydroxamates directly and avoids the formation of a five-membered ring. Thus, some of the primary limitations are overcome in this new reaction protocol.

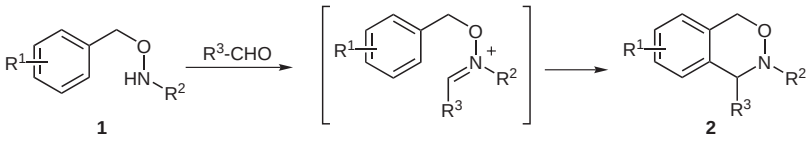


3 **5** **4**

Scheme 2

The required hydroxamates **1** for this approach were conveniently prepared in high yields according to a reported process in three steps from commercial materials.[11]

Initial attention was focused on the use of *N*-aroylhydroxamate **1a**, employing its cyclization with *n*-butyraldehyde as a model reaction, to produce compound **2a**. The conversion was further explored by looking at the use of different Lewis acids ($ZnCl_2$, $BF_3{\cdot}OEt_2$, $FeCl_3$, $TiCl_4$, $AlCl_3$ and TMSCl) and different solvent systems (CH_2Cl_2,



1 **2**

R^1 = H, OMe
R^2 = acyl, aroyl, COOMe, Ms
R^3 = H, alkyl, aryl

Scheme 1

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MeCN, THF and PhMe). Among these conditions, addition of $BF_3{\cdot}OEt_2$ to the mixture of **1a** and *n*-butyraldehyde at –78 °C, followed by warming to room temperature over a period of one hour provided the best results. In every case, the product was easily purified by silica gel flash chromatography.

These optimized conditions were subsequently applied to the reactions of *n*-butyraldehyde with different hydroxamates **1** (Table 1). Generally, electron-rich aromatic rings bearing at least two electron-donating groups are needed in order to promote the next cyclization to furnish the desired 1*H*-2,3-benzoxazines **2** (Table 1, entries 1–7). Hydroxamates bearing no or just one electron-donating group, such as **1h** and **1i**, respectively, remained unreactive towards the cyclization even in the presence of excess $BF_3{\cdot}OEt_2$ and *n*-butyraldehyde at 110 °C (Table 1, entries 9, 10). The reaction also worked with other aliphatic aldehydes such as *iso*-butyraldehyde, and the corresponding benzoxazine **2h** was isolated in 70% yield (Table 1, entry 8).[16,18] However, paraformaldehyde and aromatic aldehydes did not react under similar conditions (Table 1, entries 11, 12).

Table 1 Pictet–Spengler Cyclization Induced by $BF_3{\cdot}OEt_2$[a]

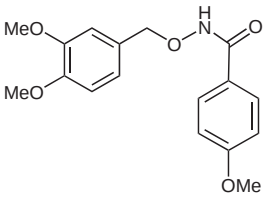
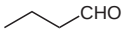
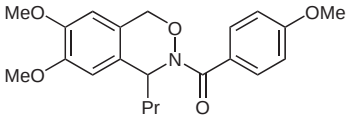
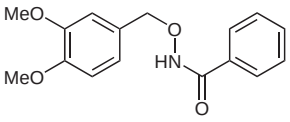
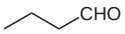
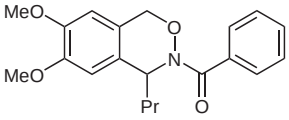
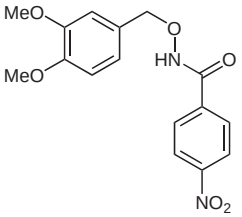
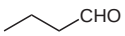
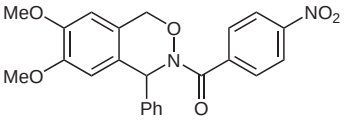
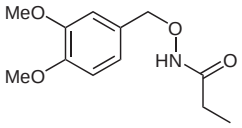
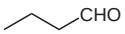
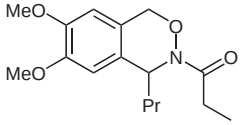
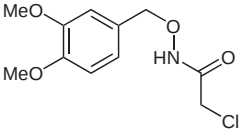
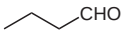
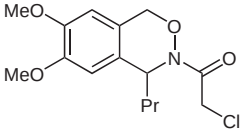
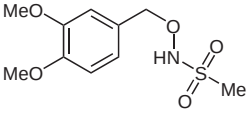
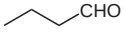
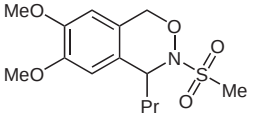
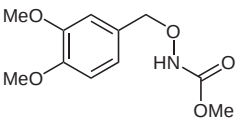
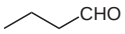
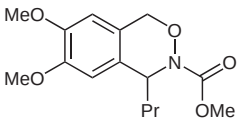
Entry	Hydroxamate	Aldehyde	Product (yield, %)[b]	Time (h)
1	 **1a**		 **2a** (98)	1
2	 **1b**		 **2b** (99)	1
3	 **1c**		 **2c** (98)	1
4	 **1d**		 **2d** (84)	1
5	 **1e**		 **2e** (89)	1
6	 **1f**		 **2f** (97)	1
7	 **1g**		 **2g** (86)	1

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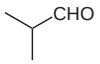
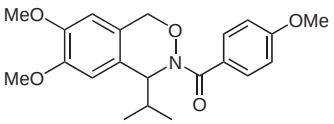
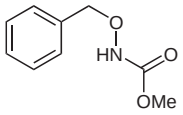
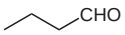
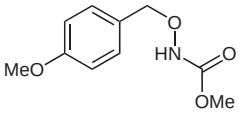
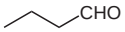
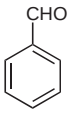
Table 1 Pictet–Spengler Cyclization Induced by $BF_3{\cdot}OEt_2$[a] (continued)

Entry	Hydroxamate	Aldehyde	Product (yield, %)[b]	Time (h)
8	**1a**		 **2h** (70)	1
9	 **1h**		(0)	24
10	 **1i**		(0)	24
11	**1a**	$(HCHO)_n$	(0)	4
12	**1a**		(0)	24

[a] Reaction conditions: $BF_3{\cdot}OEt_2$, CH_2Cl_2, –78 °C to r.t.
[b] Isolated yields.

To further extend the applicability of this Pictet–Spengler cyclization of hydroxamates **1** with aromatic aldehydes, several Lewis acids were examined. To our delight, **1a** underwent cyclization with benzaldehyde in the presence of TMSCl and NaI in MeCN at room temperature to provide **2i** in 36% yield (Table 2, entry 1).[17,18] Controlled experiments showed that TMSCl itself was not responsible for the cyclization. Various solvents were also examined, and MeCN appeared to be the best. It was believed that a facile transformation from TMSCl/NaI to TMSI occur in MeCN.[12] This result led us to explore the potential of TMSCl/NaI-catalyzed Pictet–Spengler reaction. To our delight, this catalyst system worked well with a variety of aromatic aldehydes to give the corresponding benzoxazines (Table 2, entries 1–11). Remarkably, the yields of these reactions were higher when carbalkoxyhydroxamate **1g** was utilized. Furthermore, the reaction rate was also significantly accelerated (Table 2, entries 6–10).

The importance of the electron-donating group in controlling the outcome of the reaction was also noted. Hence, both the unsubstituted **1h** and the *p*-methoxy-substituted **1i** were unreactive towards the cyclization reaction (Table 2, entries 12, 13). In contrast, the *m*-methoxy-substituted derivative **1j** produced the desired product **2s** in excellent yield (Table 2, entry 11). This was consistent with the mechanism of the cyclization (Scheme 1), in which the *m*-methoxy substitutent was correctly positioned to facilitate the nucleophilic attack of the oxoiminium ion via the carbon atom *para* to the methoxy substituent.

Table 2 Pictet–Spengler Cyclization Induced by TMSCl/NaI[a]

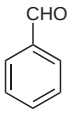
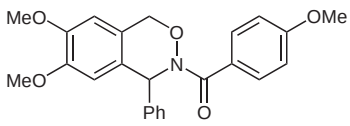
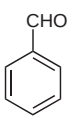
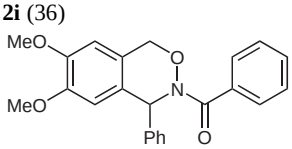
Entry	Hydroxamate	Aldehyde	Product (yield, %)[b]	Time
1	**1a**		 **2i** (36)	6 h
2	**1b**		 **2j** (32)	7 h

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Table 2 Pictet–Spengler Cyclization Induced by TMSCl/NaI[a] (continued)

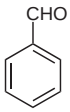
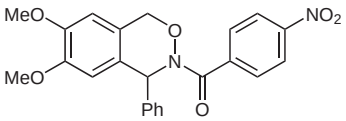
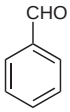
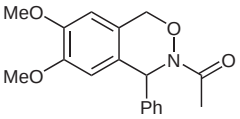
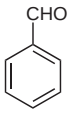
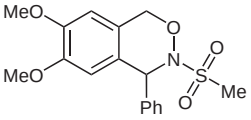
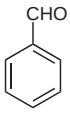
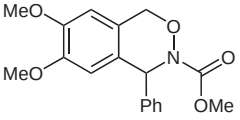
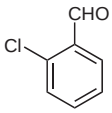
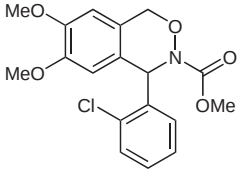
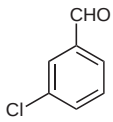
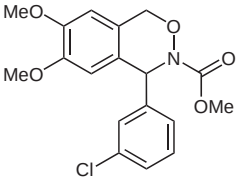
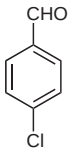
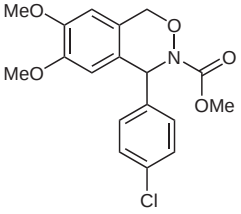
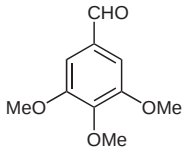
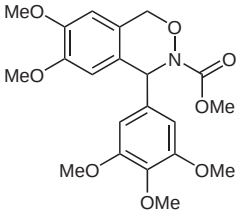
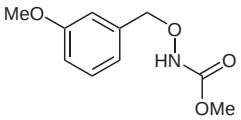
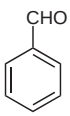
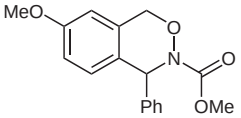
Entry	Hydroxamate	Aldehyde	Product (yield, %)[b]	Time
3	**1c**		 **2k** (17)	24 h
4[c]	**1e**		 **2l** (44)	6 h
5	**1f**		 **2m** (54)	10 h
6	**1g**		 **2n** (99)	5 min
7	**1g**		 **2o** (94)	5 min
8	**1g**		 **2p** (98)	5 min
9	**1g**		 **2q** (94)	5 min
10	**1g**		 **2r** (73)	5 min
11	 **1j**		 **2s** (98)	5 min

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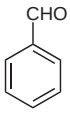
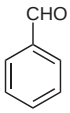
Table 2 Pictet–Spengler Cyclization Induced by TMSCl/NaI[a] (continued)

Entry	Hydroxamate	Aldehyde	Product (yield, %)[b]	Time
12	**1h**		(0)	24 h
13	**1i**		(0)	24 h

[a] Reaction conditions: TMSCl/NaI, MeCN, r.t.
[b] Isolated yields.
[c] Dechlorinated product was obtained.[13]

Interestingly, a dechlorinated product **2l** was obtained when compound **1e** was employed in the reaction (Table 2, entry 4). During the course of the reaction, both the cyclized benzoxazine **2t** and dechlorinated hydroxamate **1k** could be detected (Scheme 3). In another experiment, **2t** was also obtained from the oxime **6** in the presence of chloroacetyl chloride and KI in 1,2-dichloroethane at room temperature.[14] These findings also confirmed the formation of oxoiminium ion[15] during these reactions.

In summary, we have developed the Pictet–Spengler reaction by using hydroxamates as a new amine prototype. Both aromatic and aliphatic aldehydes can be used to prepare a variety of 4-substituted 1*H*-2,3-benzoxazines. The success of these reactions strongly depended on the presence of electron-donating substituents on the aromatic ring.

Acknowledgment

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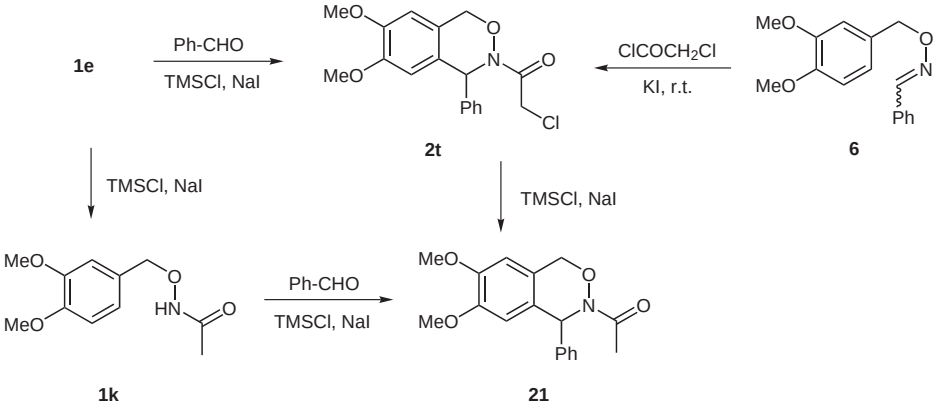

Scheme 3

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(16) **General Procedure for the Synthesis of Benzoxazines 2a–h.**
To a solution of hydroxamate **2** (0.6 mmol) in dry CH_2Cl_2 (4 mL) was added aldehyde (0.6 mmol) in one portion. The resulting mixture was chilled to –78 °C and $BF_3{\cdot}OEt_2$ (1.2 mmol) was added dropwise under N_2. The reaction mixture was allowed to warm to r.t. and quenched with Et_3N. The solvent was evaporated under reduced pressure and the residue was isolated by chromatography on silica gel to afford the desired benzoxazines **2a**–**h**.
(17) **General Procedure for the Synthesis of Benzoxazines 2i–s.**
To the solution of hydroxamate **2** (0.6 mmol) in dry MeCN (6 mL) was added aldehyde (0.9 mmol) in one portion followed by NaI (1.8 mmol) under N_2. Then, TMSCl (1.8 mmol) was added dropwise. The resulting mixture was stirred until all the hydroxamate was consumed. The resulting mixture was treated with 20% $NaHSO_3$ (6 mL) and extracted with EtOAc (3 × 10 mL). The organic phases were collected, washed (sat. $NaHCO_3$ and brine), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was isolated by chromatography on silica gel to afford the desired benzoxazines **2i**–**s**.
(18) Compound **2a**: white solid, mp 98–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H), 1.52 (br, 2 H), 1.78 (br, 1 H), 2.10 (br, 1 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 4.66, 4.76 (AB, *J* = 13.2 Hz, 2 H), 5.53 (br, 1 H), 6.40 (s, 1 H), 6.64 (s, 1 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 7.77 (br, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.17, 19.86, 38.27, 52.80, 55.46, 56.11, 56.20, 71.45, 107.22, 109.81, 113.36, 122.61, 125.78, 127.24, 131.12, 148.27, 148.44, 161.93, 168.98.
Compound **2b**: white solid, mp 109–111 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (br, 3 H), 1.58 (br, 2 H), 1.84 (br, 1 H), 2.04–2.12 (m, 1 H), 3.81 (s, 3 H), 3.89 (s, 3 H), 4.67 (br, 1 H), 4.77 (br, 1 H), 5.57 (br, 1 H), 6.43 (s, 1 H), 6.67 (s, 1 H), 7.40–7.49 (m, 3 H), 7.75 (br, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.22, 19.91, 38.33, 52.75, 56.19, 56.29, 71.70, 107.20, 109.81, 122.56, 127.17, 128.17, 128.75, 130.98, 134.07, 148.37, 148.52, 169.49.
Compound **2c**: yellow solid, mp 61–63 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.5 Hz, 3 H), 1.49–1.65 (m, 2 H), 1.85–1.91 (m, 1 H), 2.05–2.13 (m, 1 H), 3.83 (s, 3 H), 3.91 (s, 3 H), 4.70, 4.76 (AB, *J* = 13.5 Hz, 2 H), 5.57 (dd, *J* = 10.0, 3.5 Hz, 1 H), 6.44 (s, 1 H), 6.69 (s, 1 H), 7.91 (d, *J* = 8.5 Hz, 2 H), 8.29 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.18, 19.89, 38.27, 53.03, 56.21, 56.31, 72.20, 107.11, 109.70, 121.89, 123.41, 126.53, 129.80, 140.04, 148.53, 148.75, 149.15, 167.08.
Compound **2d**: white solid, mp 72–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.2 Hz, 3 H), 1.19 (t, *J* = 7.6 Hz, 3 H), 1.37–1.53 (m, 2 H), 1.70–1.79 (m, 1 H), 1.87–1.97 (m, 1 H), 2.39–2.48 (m, 1 H), 2.59–2.67 (m, 1 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.84, 5.01 (AB, *J* = 13.6 Hz, 2 H), 5.38 (dd, *J* = 9.6, 4.0 Hz, 1 H), 6.48 (s, 1 H), 6.63 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.16, 14.18, 19.73, 25.66, 38.38, 52.22, 56.14, 56.22, 71.64, 107.10, 109.76, 122.70, 127.33, 148.19, 148.43, 172.80.
Compound **2e**: white solid, mp 115–117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.0 Hz, 3 H), 1.34–1.52 (m, 2 H), 1.73–1.80 (m, 1 H), 1.88–1.96 (m, 1 H), 3.86 (s, 3 H), 3.86 (s, 3 H), 4.27, 4.33 (AB, *J* = 13.0 Hz, 2 H), 4.89 (d, *J* = 13.5 Hz, 1 H), 5.14 (d, *J* = 13.5 Hz, 1 H), 5.33 (dd, *J* = 9.5, 4.0 Hz, 1 H), 6.48 (s, 1 H), 6.61 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.17, 19.61, 38.42, 40.92, 53.20, 56.22, 56.30, 72.42, 107.05, 109.63, 122.16, 126.35, 148.46, 148.64, 165.01.
Compound **2f**: white solid, mp 121–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.0 Hz, 3 H), 1.48–1.56 (m, 2 H), 1.75–1.82 (m, 1 H), 1.92–1.99 (m, 1 H), 3.12 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.83 (dd, *J* = 9.0, 5.0 Hz, 1 H), 4.84, 5.43 (AB, *J* = 14.0 Hz, 2 H), 6.49 (s, 1 H), 6.60 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.07, 19.85, 38.27, 39.30, 54.82, 56.15, 56.26, 69.37, 107.01, 109.63, 122.25, 125.63, 148.21, 148.61.
Compound **2g**: white solid, mp 60–61 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 3 H), 1.39–1.46 (m, 2 H), 1.60–1.67 (m, 1 H), 1.86–1.93 (m, 1 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 4.67, 4.88 (AB, *J* = 14.0 Hz, 2 H), 5.06 (d, *J* = 14.0 Hz, 1 H), 6.42 (s, 1 H), 6.54 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.02, 19.82, 38.06, 53.29, 55.83, 56.14, 56.22, 69.96, 107.28, 109.52, 123.18, 127.07, 148.23, 148.29, 155.95.
Compound **2h**: white solid, mp 113–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 9.0 Hz, 3 H), 1.16 (d, *J* = 6.0 Hz, 3 H), 2.28–2.35 (m, 1 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 4.65, 4.71 (AB, *J* = 13.0 Hz, 2 H), 5.43 (br, 1 H), 6.42 (s, 1 H), 6.72 (s, 1 H), 6.92 (d, *J* = 8.5 Hz, 2 H), 7.83 (br d, *J* = 6.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.15, 20.34, 34.53, 55.55, 56.14, 56.24, 57.31, 71.31, 107.05, 110.46, 113.34, 123.24, 125.75, 125.96, 131.26, 148.15, 148.34, 161.86, 169.44.
Compound **2i**: white solid, mp 115–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.84, 5.01 (AB, *J* = 13.6 Hz, 2 H), 6.54 (s, 1 H), 6.59 (s, 1 H), 6.66 (s, 1 H), 6.90 (dd, *J* = 9.2, 2.4 Hz, 2 H), 7.29–7.75 (m, 5 H), 7.77 (dd, *J* = 9.2, 2.4 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.58, 56.21, 56.24, 56.53, 71.58, 106.91, 110.86, 113.40, 123.49, 124.78, 125.71, 128.15, 128.66, 129.16, 131.22, 140.99, 148.70, 148.73, 162.05, 168.46.
Compound **2j**: white solid, mp 125–127 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.77 (s, 3 H), 3.86 (s, 3 H), 4.86, 5.00 (AB, *J* = 14.0 Hz, 2 H), 6.54 (s, 1 H), 6.58 (s, 1 H), 6.65 (s, 1 H), 7.26–7.69 (m, 10 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.97, 55.9, 56.36, 71.51, 106.70, 110.58, 123.20, 124.38, 127.91, 127.99, 128.45, 128.51, 128.88, 130.88, 133.58, 140.59, 148.51, 148.54, 168.64.
Compound **2k**: white solid, mp 191–197 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.78 (s, 3 H), 3.88 (s, 3 H), 4.85, 4.95 (AB, *J* = 14.0 Hz, 2 H), 6.55 (s, 1 H), 6.58 (s, 1 H), 6.66 (s, 1 H), 7.34–7.43 (m, 5 H), 7.83 (dd, *J* = 7.0, 2.0 Hz, 2 H), 8.25 (dd, *J* = 7.0, 2.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 56.02, 56.04, 56.26, 71.99, 106.62, 110.49, 122.59, 123.17, 123.81, 128.33, 128.62, 128.90, 129.55, 139.55, 140.12, 148.71, 148.80, 148.98, 166.20.
Compound **2l**: white solid, mp 170–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.16 (s, 3 H), 3.76 (s, 3 H), 3.89 (s, 3 H), 4.98, 5.14 (AB, *J* = 13.6 Hz, 2 H), 6.51 (s, 1 H), 6.53 (s, 1 H), 6.59 (s, 1 H), 7.28–7.35 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.52, 55.34, 56.22, 71.84, 106.88, 110.78, 123.62, 124.74, 128.21, 128.63, 129.10, 140.93, 148.66, 148.78, 169.08.

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Compound **2m**: white solid, mp 134–136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 3.73 (s, 3 H), 3.89 (s, 3 H), 5.06, 5.40 (AB, *J* = 13.5 Hz, 2 H), 5.78 (s, 1 H), 6.43 (s, 1 H), 6.62 (s, 1 H), 7.34–7.41 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.79, 56.20, 56.21, 61.92, 72.71, 106.74, 110.69, 123.99, 125.81, 128.77, 129.10, 130.38, 137.78, 148.72, 148.74.

Compound **2n**: white solid, mp 113–115 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 4.92, 5.22 (AB, *J* = 14.0 Hz, 2 H), 6.09 (s, 1 H), 6.52 (s, 1 H), 6.60 (s, 1 H), 7.27–7.37 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.45, 56.20, 59.08, 70.94, 107.02, 110.61, 124.16, 124.79, 128.24, 128.62, 129.05, 140.64, 148.55, 148.66, 155.40.

Compound **2o**: white solid, mp 186–188 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.77 (s, 3 H), 3.80 (s, 3 H), 3.87 (s, 3 H), 4.91, 5.23 (AB, *J* = 14.0 Hz, 2 H), 6.59 (s, 1 H), 6.60 (s, 1 H), 6.64 (s, 1 H), 7.15–7.43 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.62, 55.34, 5.18, 56.19, 70.16, 107.14, 110.00, 123.72, 124.63, 127.38, 129.37, 129.71, 130.83, 133.55, 138.95, 148.78, 155.50.

Compound **2p**: white solid, mp 127–129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.77 (s, 3 H), 3.81 (s, 3 H), 3.89 (s, 3 H), 4.92, 5.21 (AB, *J* = 14.0 Hz, 2 H), 6.04 (s, 1 H), 6.49 (s, 1 H), 6.60 (s, 1 H), 7.25–7.33 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.56, 56.22, 56.25, 58.53, 70.92, 107.15, 110.50, 124.04, 124.18, 127.29, 128.50, 129.18, 129.87, 134.51, 142.53, 148.69, 148.90, 155.29.

Compound **2q**: white solid, mp 57–59 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3 H), 3.80 (s, 3 H), 3.88 (s, 3 H), 4.91, 5.21 (AB, *J* = 13.8 Hz, 2 H), 6.05 (s, 1 H), 6.48 (s, 1 H), 6.60 (s, 1 H), 7.26–7.31 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.51, 56.20, 58.41, 70.98, 107.09, 110.46, 124.18, 124.32, 128.78, 130.47, 134.18, 139.11, 148.66, 148.81, 155.34.

Compound **2r**: white solid, mp 150–151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.79 (s, 6 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 4.92–5.20 (AB, *J* = 13.8 Hz, 2 H), 6.02 (s, 1 H), 6.56 (s, 1 H), 6.58 (s, 2 H), 6.60 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.50, 56.18, 56.26, 56.34, 56.44, 59.10, 60.99, 70.91, 106.23, 107.00, 110.63, 124.09, 124.53, 136.34, 138.02, 148.52, 148.70, 153.27, 155.36.

Compound **2s**: white solid, mp 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.79 (s, 3 H), 3.80 (s, 3 H), 4.96, 5.25 (AB, *J* = 14.0 Hz, 2 H), 6.11 (s, 1 H), 6.64 (d, *J* = 2.5 Hz, 1 H), 6.79 (dd, *J* = 8.5, 2.5 Hz, 1 H), 6.99 (d, *J* = 8.5 Hz, 1 H), 7.26–7.36 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.47, 55.58, 59.14, 71.42, 109.18, 113.94, 125.13, 128.16, 128.59, 128.95, 129.38, 133.30, 140.95, 155.41, 158.77.

Compound **2t**: white solid, mp 180–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (s, 3 H), 3.90 (s, 3 H), 4.12, 4.34 (AB, *J* = 13.2 Hz, 2 H), 5.02, 5.28 (AB, *J* = 13.6 Hz, 2 H), 6.44 (s, 1 H), 6.52 (s, 1 H), 6.60 (s, 1 H), 7.30–7.37 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.30, 56.24, 56.48, 72.53, 106.80, 110.67, 123.21, 124.00, 128.52, 128.73, 129.18, 140.25, 148.83, 148.92, 164.87.

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