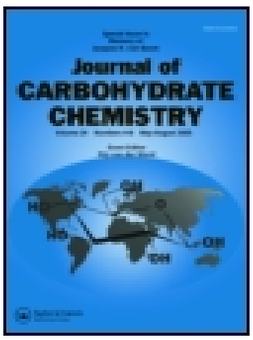

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Eco-friendly synthesis of 5-hydroxymethylfurfural (HMF) and its application to the Ferrier-rearrangement reaction

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Eco-friendly synthesis of 5-hydroxymethylfurfural (HMF) and its application to the Ferrier-rearrangement reaction

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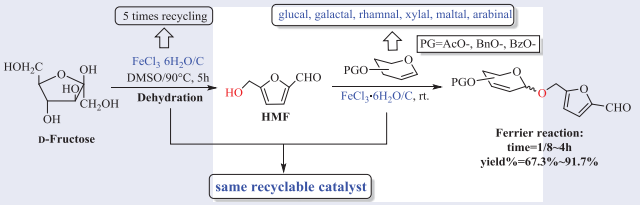
ABSTRACT

5-Hydroxymethylfurfural was conveniently synthesized by dehydration of D-fructose in a good yield. To further build bioactive derivatives from 5-hydroxymethylfurfural, 2,3-unsaturated glycosides were directly obtained through the Ferrier-rearrangement reaction of various glycals. Noticeably, a solid acid catalyst was successfully applied in the preparation of 5-hydroxymethylfurfural and then recycled to promote the Ferrier-rearrangement reaction, making it possible to achieve two steps of reaction in an eco-friendly manner through the simple process.

GRAPHICAL ABSTRACT



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Ferrier-rearrangement reaction; glycal; recyclable; solid acid catalyst; 2,3-unsaturated glycoside; 5-hydroxymethylfurfural

Introduction

5-Hydroxymethylfurfural (HMF) as a significant platform compound and valuable molecule can be obtained from carbohydrates such as fructose, sucrose, cellulose or from biomass materials.[1–14] For example, HMF shows its value not only as a material for the production of dimethylfuran (DMF) and other important molecules such as levulinic acid, 2,5-furandicarboxylic acid (FDA), and 2,5-diformylfuran (DFF),[3–5,13–15] but also as an abundant constituent widely distributed in traditional Chinese medicine such as processed steamed *Rehmanniae Radix*, a Chinese medicine used to treat several diseases, including anemia and diabetes. In recent studies, HMF also showed good antibacterial properties.[16]

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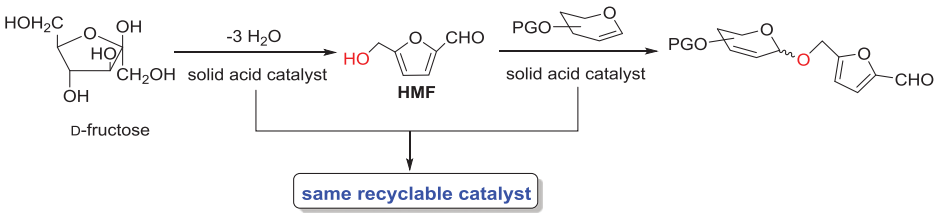


Scheme 1. Preparation of 2,3-unsaturated glycosides with recyclable catalyst.

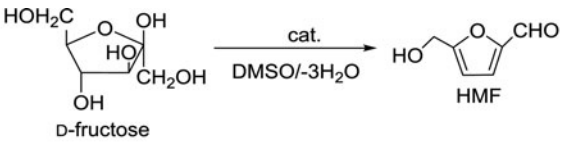
Additionally, 2,3-unsaturated sugars that can be obtained through Ferrier reaction are significant intermediates in the synthesis of natural products and bioactive molecules.[17–22] Based on the admirable reactivity of HMF, which can be expected to react in the presence of glycals to obtain a series of pharmaceutical products, we attempt to achieve HMF and its glycosylation reaction with the same recyclable catalyst (Sch. 1), inspired by our previous work in the area.[20,23–27]

Results and discussion

Although HMF is commercially available and various preparation methods have been developed in the past few decades, we were dedicated to develop a greener and more efficient synthetic method toward HMF. There is still room for further improvement of previously reported solid acid catalyst applied in synthesizing HMF, e.g., to avoid toxicity, high price, and complicated preparation. In order to find out an efficient and available catalyst and circumvent the aforementioned problems, we test various low or non-toxic acid catalysts, including inorganic Brønsted acid such as HCl, H_3BO_3, NaH_2PO_4, H_2MoO_4, and so on,[2,10–11,14,28] organic Brønsted acid such as propyl sulfonic acid, propionic acid, acrylic acid, benzoic acid, alanine, etc.,[29–31] and Lewis acid such as $ZnCl_2$, $FeCl_3$, $FeCl_3{\cdot}6H_2O$, and $CrCl_3$. Their efficiencies to catalyze the transformation of D-fructose to HMF are shown in Figure 1. [32,33]

Thereafter, different catalytic systems and immobilization ratios of solid acid catalysts were tested, based on previous exploration.[20,25–27] Along with solid super acids, a strongly acidic cation exchange resin, *p*-TsOH·H_2O, $FeCl_3$, and $FeCl_3{\cdot}6H_2O$, which also showed high catalytic activities, was selected for further immobilization experiments as well. As shown in Table 1, H_2SO_4 and *p*-TsOH·H_2O loaded onto SiO_2 failed to provide satisfactory catalytic performance (entry 1–4), and solid super acid (entry 5) was hardly applied to this reaction. Although activation with strong-acid cation exchange resin (entry 6) afforded HMF in a 72% yield, the adsorption on the surface of resin by polymeric by-products was observed, which led to the catalyst poisoning and seriously impeded the catalyst recycling. The results also indicated that $FeCl_3{\cdot}6H_2O$ was superior to $FeCl_3$ as a Fe^{3+} source (entry 7–14). Obviously, $FeCl_3{\cdot}6H_2O$/C (2 g:3 g) (entry 12) had the highest efficiency to catalyze the dehydration reaction of D-fructose in dimethyl sulfoxide (DMSO).

To improve the result of the catalysts further, different solvents were examined, with optimal condition observed employing 0.1 equivalent of $FeCl_3{\cdot}6H_2O$/C



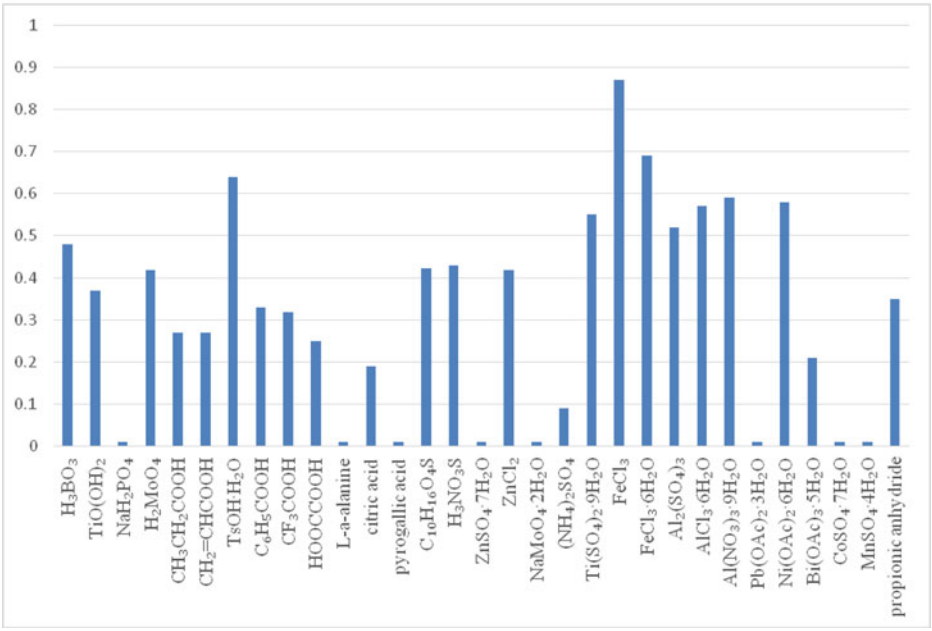


Figure 1. The efficiencies of various acid catalysts applied to D-fructose dehydration.

(2 g:3 g) at 90°C. Clearly, the results (Table 2) indicated that DMSO (entry 1) was the best solvent, whereas polyethylene glycol 400 (PEG 400) (entry 1) was comparable.

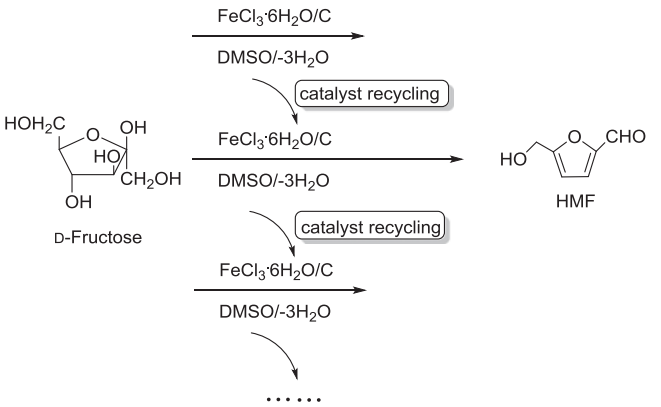
Besides, experiments were also carried out to explore the recyclability of solid acid catalyst (Sch. 2). It was clearly demonstrated in Table 3 that the yields remained steady (77%) in the first three recycles but declined slowly thereafter. Delightfully, this catalyst still gave an acceptable yield (62%) in the fifth recycle, suggesting that it

Table 1. Efficiencies of different solid acids to catalyze D-fructose dehydration in DMSO.

Entry	Catalyst	Yield (%)
1	H_2SO_4/SiO_2 (2 mL:10 g)	60
2	H_2SO_4/SiO_2 (3 mL:10 g)	65
3	$TsOH/SiO_2$ (2 g:5 g)	50
4	$TsOH/SiO_2$ (5 g:5 g)	60
5	SO_4^{2-}/ZrO_2 (1:2)	39
6	Cation exchange resin FPC11Na	72
7	$FeCl_3/C$ (1 g:5 g)	15
8	$FeCl_3/C$ (3 g:5 g)	20
9	$FeCl_3/C$(5 g:5 g)	25
10	$FeCl_3 \cdot 6H_2O/C$ (0.5 g:3 g)	65
11	$FeCl_3 \cdot 6H_2O/C$ (1 g:3 g)	70
12	$FeCl_3 \cdot 6H_2O/C$ (2 g:3 g)	77
13	$FeCl_3 \cdot 6H_2O/C$ (3 g:3 g)	75
14	$FeCl_3 \cdot 6H_2O/C$ (6 g:3 g)	73

Table 2. The catalytic performance of $FeCl_3 \cdot 6H_2O$/C in different solvents.

Entry	Solvent	Yield (%)
1	DMSO	77
2	PEG 400	72
3	1,4-dioxane	24
4	Cyclohexanol	23
5	2-Butanol	8
6	n-Butanol	5
7	Acetonitrile	4



Scheme 2. Use of recyclable catalyst in the preparation of HMF.

can meet the requirements of green chemistry and be further developed for industrial mass production.

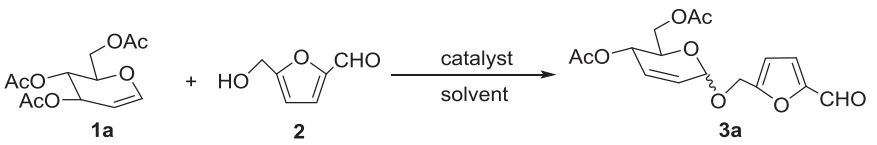
Considering that most metal Lewis acid catalysts used in the Ferrier-rearrangement reaction usually present similar problems such as high price and toxicity, not being environmentally friendly, etc.,[34–42] our group has explored previously $FeCl_3$ and $FeCl_3 \cdot 6H_2O$ as glycosylation promoters, especially in Ferrier-rearrangement reactions, to attain satisfactory results.[20,24,43,44] Further, immobilization of homogeneous catalysts can also solve operational and moisture-absorption problems.[20,26,27] Inspired by these studies and the reactivity of the OH group in HMF, the same catalyst used to generate HMF under optimal conditions was explored for Ferrier-type glycosylation to directly build 2,3-unsaturated glycosides (Table 4).[45–48] Initially, DMSO and PEG 400 were used as solvents, which did not give satisfactory results and were also difficult to achieve one-pot method (entries 1 and 2). Persistently, we focused on using the same recyclable catalyst in other solvents to simplify operational process. Thus, different common solvents, such as CH_3CN, dichloromethane (DCM) and dichloroethane (DCE) applied into the Ferrier reaction were explored (entries 3–5),[23,26,27] and it was found that using

Table 3. Efficiencies of recycled catalyst in preparation of HMF.

Run	1	2	3	4	5
Yields (%)[a]	77	77	77	69	62

[a]Reaction time was 5 h.

Table 4. Optimization of Ferrier-type glycosylation of acceptor **2** with donor **1a.**

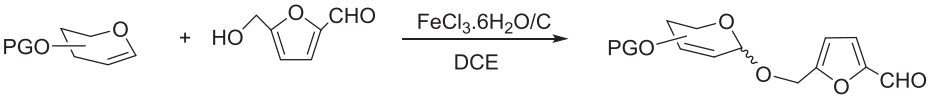


Entry	Solvent	Eq. (D:A)	Eq. (cat.)	*T* (°C)	Time (h)	Yield (%)
1	DMSO	1:4	1	rt	24	Trace
2	PEG 400	1:4	1	rt	24	nd
3	CH_3CN	1:4	1	rt	24	10
4	DCM	1:4	1	rt	2.5	70
5	DCE	1:4	1	rt	0.16	75
6	DCE	1:2	1	rt	0.16	80
7	DCE	1:1	1	rt	0.16	80
8	DCE	1:1.2	1	rt	0.16	85
9	DCE	1:1.2	0.5	rt	0.16	85
10	DCE	1:1.2	0.2	rt	0.16	85
11	DCE	1:1.2	0.1	rt	0.16	85
12	DCE	1:1.2	0.05	rt	0.16	85
13	DCE	1:1.2	0.02	rt	1	30
14	DCE	1:1.2	0.1	40	0.16	80

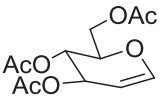
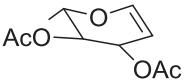
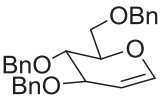
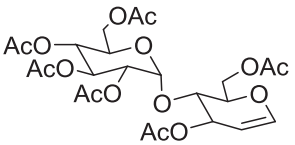
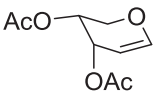
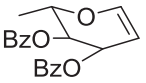
DCE as solvent led to a higher yield in a short reaction time at room temperature (entry 5). Then, a screen of various equivalent ratios of donor **1a** and acceptor **2** revealed that an acceptor/donor equivalent ratio of 1.2/1 was optimal (entry 8) and that a decrease of equivalent ratio was detrimental for the yield of **3a** (entry 7). We postulated that excess acceptor (entry 6) might bring about complexation with catalyst, thus reducing the yield of product.[44] Modifying the equivalent of catalyst ranging from 1 to 0.05 equivalent was shown to retain the same yield (85%, entries 8–12), until it was decreased to 0.02 equivalent, which afforded an unsatisfactory result (30%, entry 13). In view of the fact that the previous step (Fig. 1) also employed 0.1 equivalent of catalyst and the catalyst was recyclable, we chose 0.1 equivalent of $FeCl_3 \cdot 6H_2O$/C as the optimal amount of catalyst for this reaction (entry 12). Besides, an elevation of the impact of temperature revealed that increased temperature, 40°C *vs* room temperature, had a hindering effect (entry 14).

Having established the optimal reaction conditions, we decided to expand the glycosylation method for different glycals (Table 5).[49] We were eager to see whether the high yield observed for product **3a** could be translated to other types of 2,3-unsaturated glycosides to provide more derivatives from HMF and further expand its pharmaceutical value. Thus, a diverse range of glycals including glucal, galactal, rhamnal, xylal, maltal, and arabinal with different protecting groups such as acetyl, benzyl, and benzoyl groups were explored to afford the desired glycosylated products in good to excellent yields (67–92%) and the anomeric ratio (α:β) ranged from 5:1 to only α. The glycosylations were also fairly quick (7 min to 4 h), especially the reaction time of compound **1a** could be shortened from 24 h to 10 min, compared with the reported data (Table 5, entry 1).[45,47] These results demonstrated that the catalyst and the optimal reaction condition are broadly applicable to different glycal donors and have thus built the foundation for the synthesis of natural bioactive molecules and their analogs through the Ferrier-rearrangement reaction.

Table 5. The scope of $FeCl_3 \cdot 6H_2O$/C-catalyzed Ferrier-type glycosylation using different glycals.



1a-h **2** **3a-h**

Entry	Donors	Time (h)	Yield (%),[a] α:β
1	**1a** 	0.16	82%, 7:1
2	**1b** 	2	86%, 7:1
3	**1c** 	0.16	92%, 8:1
4	**1d** 	3.5	77%, 5:1
5	**1e** 	0.16	92%, 5:1
6	**1f** 	4	85%, 5:1
7	**1g** 	0.12	87%, >19.1
8	**1h**	1	67%, 5:1

[a]The anomeric ratio was determined by ^{1}H NMR spectra.

Besides, a recent study showed that the derivatives of HMF possess different kinds of biological activity and some of them are even more active than HMF.[50,51] Based on this consideration, we preliminarily studied the antitumor activity (*in vitro* against the K_{562} cell line)[20,52] of the 2,3-unsaturated glycosdies derived from HMF and evaluated their structure–activity relationship. We found that isomerization at the C-4 position, glucal **3a** *vs* galactal **3b** (the former was more potent), glycosyl substitution at C-4, **3a** *vs* **3f** (substitution had an inhibitory effect), and difference

Table 6. *In vitro* antitumor activities of glycosidic HMF derivatives against the K_{562} cell line.[a]

Entry	Compound	Concentration (μg/mL)	Inhibition rate (%)
1	Cisplatin	10	47.0
2	**3a**	100	11.4
3	**3b**	100	− 2.2
4	**3c**	100	− 0.3
5	**3d**	100	25.5
6	**3f**	100	7.9
7	**3g**	100	41.3
8	**3h**	100	71.0

[a]DMSO was used as solvent.

in protecting groups, **3a** *vs* **3d** (OBn was better than OAc) and **3c** *vs* **3h** (OBz was better than OAc) could all influence the antitumor activity. Form these results, we concluded that compounds **3g** and **3h** derived from acetyl-arabinal and benzoyl-rhamnal, respectively, showed promising antitumor activities (Table 6, entries 7 and 8). Further orthogonal research on the antitumor activities of different types of glycals and protecting groups is undergoing.

Conclusion

In summary, we have developed a novel method to achieve HMF from D-fructose and its Ferrier-type glycosylation by using the same recyclable catalyst through a simple operational process. This method boasts several remarkable features, most significantly employing a recyclable, low-toxic and easily accessible solid acid catalyst $FeCl_3 \cdot 6H_2O/C$ for both steps, which can greatly simplify experimental procedure and meet the concept of green chemistry. Besides, this Ferrier-type glycosylation offers a new method for rapid and efficient synthesis of various 2, 3-unsaturated glycosides in good to excellent yields, which possess potential bioactivity and pharmaceutical values.

Experimental

General methods: ^1H and ^{13}C NMR spectra were recorded using a 500 MHz spectrometer with tetramethylsilane (TMS) as internal standard. Mass spectra were detected using an Agilent 5973N EI mass spectrometer. All the reactions were monitored using thin layer chromatography (TLC) on silica gel HF_{254} [10–40 μm, Yantai, China (0.2 mm)]. Reaction products were purified by flash chromatography using silica gel 60 (300–400 mesh or 200–300 mesh, Yantai, China).

Procedure for the preparation of 5-hydroxymethylfurfural (HMF: D-Fructose (0.18 g, 1 mmoL) and $FeCl_3 \cdot 6H_2O/C$ (67.5 mg, 0.1 mmoL) were dissolved in 2 mL of DMSO and stirred for 5 h with an oil bath heated at 90°C. Then, the mixture was filter out through to remove the catalyst, which can be employed in the next step. The solution was extracted with ethyl acetate (6 × 30 mL), and the solvent was evaporated. The product could be employed in the next reaction directly for one-pot synthesis. Also, the residue was purified by column chromatography (4:1 petroleum

ether/ EtOAc) to obtain HMF as brownish yellow syrupy (97 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.55 (s, 1 H), 7.20 (d, J = 3.5 Hz, 1 H), 6.50 (d, J = 3.5 Hz, 1 H), 4.69 (s, 2 H), and 3.08 (s, 1 H). High resolution mass spectrum (HRMS) (ESI$^+$): m/z calcd. for $C_6H_6O_3Na$ $[M+Na]^+$ 149.0209, found 149.0205.

General procedure for the preparation of unsaturated sugar glycosides 3a–h: To a mixture of 3,4,6-tri-O-acetyl-D-glucal (1 mmoL) and HMF (1.2 mmol) in DCE (10 mL) was added the catalyst, which was followed by stirring at rt. The reaction was monitored by TLC (PE/EA 1.0/1.0 v/v). After the reaction is finished, it was filtered on a Celite pad. The solution was concentration and the raw product was purified on a silica gel column (CH_2Cl_2) to give a mixture of α and β anomers.

3a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62 (s, 1 H), 7.21 (d, J = 3.5 Hz, 1 H), 6.55 (d, J = 3.5 Hz, 1 H), 6.03 (dd, J = 11.7, 3.8 Hz, 1 H), 5.92 (d, J = 10.2 Hz, 1 H), 5.87–5.79 (m, 1 H), 5.34 (dd, J = 9.7, 1.4 Hz, 1 H), 5.24 (s, 1 H), 5.15 (s, 1 H), 4.84 (d, J = 13.3 Hz, 1 H), 4.78 (d, J = 13.3 Hz, 1 H), 4.66 (t, J = 12.6 Hz, 1 H), 4.25 (dd, J = 12.2, 5.1 Hz, 1 H), 4.17 (dd, J = 12.2, 2.4 Hz, 1 H), 4.14–4.07 (m, 1H), 2.10 (s, 3 H), 2.08 (s, 4 H). Low resolution mass spectrum (LRMS) (ESI$^+$): *m/z* calcd. for $C_{16}H_{18}O_8Na$ $[M+Na]^+$ 361.09, found 361.08.

3b: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62 (d, J = 1.3 Hz, 1 H), 7.21 (d, J = 3.5 Hz, 1 H), 6.55 (d, J = 3.5 Hz, 1 H), 6.16 (dd, J = 10.0, 5.5 Hz, 1 H), 6.03 (dd, J = 10.0, 3.0 Hz, 1 H), 5.18 (d, J = 2.9 Hz, 1 H), 5.04 (dd, J = 5.4, 2.1 Hz, 1 H), 4.78 (d, J = 13.3 Hz, 1 H), 4.66 (d, J = 13.3 Hz, 1 H), 4.40–4.33 (m, 1 H), 4.26 – 4.21 (m, 2 H), 2.08 (d, J = 1.4 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.73, 170.60, 170.30, 157.42, 152.87, 129.82, 125.88, 121.71, 111.69, 93.38, 67.11, 62.63, 62.54, 61.54, 20.80, 20.79. HRMS (ESI$^+$): *m/z* calcd. for $C_{16}H_{18}O_8Na$ $[M+Na]^+$ 361.0899, found 361.0894.

3c: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62 (d, J = 4.0 Hz, 1 H), 7.20 (t, J = 3.4 Hz, 1 H), 6.54 (d, J = 3.5 Hz, 1 H), 5.88 (d, J = 10.3 Hz, 1 H), 5.80 (dt, J = 10.3, 2.2 Hz, 1 H), 5.24 (d, J = 1.6 Hz, 1 H), 5.06 (dd, J = 12.2, 1.8 Hz, 2 H), 4.82 (d, J = 13.3 Hz, 1 H), 4.76 (d, J = 13.4 Hz, 1 H), 4.66 (t, J = 12.0 Hz, 1 H), 3.95 (tt, J = 17.9, 6.2 Hz, 1 H), 2.08 (s, 3 H), 1.33 (d, J = 6.6 Hz, 1 H), 1.20 (d, J = 6.3 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.76, 170.53, 158.07, 152.84, 130.46, 126.99, 121.91, 111.45, 94.22, 70.70, 65.23, 62.03, 21.05, 17.91. HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{16}O_6Na$ $[M+Na]^+$ 303.0845, found 303.0836.

3d: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62–9.57 (m, 1 H), 7.35–7.27 (m, 10 H), 7.25 (d, J = 6.7 Hz, 2 H), 7.16 (d, J = 3.5 Hz, 1 H), 6.50 (d, J = 3.3 Hz, 1 H), 6.10 (t, J = 10.3 Hz, 1 H), 5.86 (dd, J = 10.3, 1.4 Hz, 1 H), 5.80–5.74 (m, 1 H), 5.24 (s, 1 H), 5.14 (s, 1 H), 4.83 (d, J = 13.4 Hz, 1 H), 4.79 (d, J = 13.4 Hz, 1 H), 4.69 (s, 1 H), 4.66 (d, J = 3.1 Hz, 1 H), 4.62 (d, J = 7.7 Hz, 1 H), 4.60–4.55 (m, 1 H), 4.52 (d, J = 12.1 Hz, 1 H), 4.45 (d, J = 11.5 Hz, 1 H), 4.19 (d, J = 9.4 Hz, 1 H), 4.00–3.93 (m, 1 H), 3.74 (dd, J = 10.7, 4.1 Hz, 1 H), 3.70–3.66 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.90, 158.26, 152.81, 138.21, 138.05, 131.56, 128.53, 128.50, 127.98, 127.94, 127.81,

127.11, 125.89, 121.84, 111.56, 94.48, 73.56, 71.30, 70.32, 69.69, 68.84, 62.04. HRMS (ESI^+): *m/z* calcd. for $C_{26}H_{26}O_6Na$ $[M+Na]^+$ 457.1627, found 457.1624.

3e: ^1H NMR (500 MHz, $CDCl_3$): δ 9.63 (s, 1 H), 7.21 (d, $J = 3.2$ Hz, 1 H), 6.54 (d, $J = 3.1$ Hz, 1 H), 6.12 (dd, $J = 9.7$, 5.2 Hz, 1 H), 6.04 (dd, $J = 10.0$, 2.6 Hz, 1 H), 5.12 (s, 1 H), 4.96 (s, 1 H), 4.77 (d, $J = 13.3$ Hz, 1 H), 4.65 (d, $J = 13.3$ Hz, 1 H), 4.16 (dd, $J = 12.9$, 2.0 Hz, 1 H), 3.86 (d, $J = 13.0$ Hz, 1 H), 2.10 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.91, 170.82, 157.74, 152.98, 130.22, 125.77, 111.83, 92.78, 63.18, 61.85, 61.63, 21.22. HRMS (ESI^+): *m/z* calcd. for $C_{13}H_{14}O_6Na$ $[M+Na]^+$ 289.0688, found 289.0681.

3f: ^1H NMR (500 MHz, $CDCl_3$): δ 9.64 (s, 1 H), 7.22 (d, $J = 3.4$ Hz, 1 H), 6.57 (d, $J = 3.3$ Hz, 1 H), 5.89 (d, $J = 10.4$ Hz, 1 H), 5.83 (d, $J = 10.3$ Hz, 1 H), 5.41 (t, $J = 10.0$ Hz, 1 H), 5.31 (d, $J = 3.7$ Hz, 1 H), 5.10 (d, $J = 11.7$ Hz, 1 H), 5.06 (d, $J = 9.6$ Hz, 1 H), 4.83 (dd, $J = 10.1$, 3.5 Hz, 1 H), 4.78 (d, $J = 13.3$ Hz, 1 H), 4.65 (d, $J = 13.2$ Hz, 1 H), 4.34 (dd, $J = 6.6$, 3.5 Hz, 2 H), 4.28 (d, $J = 3.2$ Hz, 1 H), 4.25 (d, $J = 4.2$ Hz, 1 H), 4.08 (s, 1 H), 4.06 (s, 2 H), 2.13 (s, 3 H), 2.10 (s, 4 H), 2.06 (s, 4 H), 2.03 (s, 4 H), 2.01 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.89, 170.75, 170.73, 170.42, 170.14, 169.70, 157.59, 152.97, 129.31, 127.20, 121.95, 111.83, 94.18, 93.99, 70.88, 69.89, 69.63, 68.35, 68.27, 67.81, 63.25, 62.14, 61.78, 20.97, 20.81, 20.79, 20.78, 20.73. HRMS (ESI^+): *m/z* calcd. for $C_{28}H_{34}O_{16}Na$ $[M+Na]^+$ 649.1745, found 649.1742.

3g: ^1H NMR (500 MHz, $CDCl_3$): δ 9.63 (s, 1 H), 7.21 (d, $J = 3.4$ Hz, 1 H), 6.54 (d, $J = 3.4$ Hz, 1 H), 6.12 (dd, $J = 9.9$, 5.2 Hz, 1 H), 6.04 (dd, $J = 10.1$, 2.9 Hz, 1 H), 5.12 (d, $J = 2.7$ Hz, 1 H), 4.98–4.94 (m, 1 H), 4.77 (d, $J = 13.3$ Hz, 1 H), 4.65 (d, $J = 13.3$ Hz, 1 H), 4.16 (dd, $J = 13.0$, 2.6 Hz, 1 H), 3.86 (d, $J = 13.0$ Hz, 1 H), 2.09 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.91, 170.72, 157.74, 152.98, 130.22, 125.77, 121.88, 111.84, 92.78, 63.18, 61.85, 61.63, 21.22. HRMS (ESI^+): *m/z* calcd. for $C_{13}H_{14}O_6Na$ $[M+Na]^+$ 289.0688, found 289.0683.

3h: ^1H NMR (500 MHz, $CDCl_3$): δ 9.64 (s, 1 H), 8.03 (d, $J = 8.0$ Hz, 2 H), 7.58 (t, $J = 7.4$ Hz, 1 H), 7.45 (t, $J = 7.7$ Hz, 2 H), 7.22 (d, $J = 3.4$ Hz, 1 H), 6.57 (d, $J = 2.8$ Hz, 1 H), 6.10 (d, $J = 10.3$ Hz, 1 H), 6.02 (d, $J = 10.2$ Hz, 1 H), 5.96 (d, $J = 10.3$ Hz, 1 H), 5.87 (d, $J = 10.2$ Hz, 1 H), 5.34 (d, $J = 9.3$ Hz, 1 H), 5.14 (s, 1 H), 4.86 (d, $J = 13.4$ Hz, 1 H), 4.81 (d, $J = 13.3$ Hz, 1 H), 4.69 (d, $J = 13.3$ Hz, 1 H), 4.16 (dt, $J = 12.4$, 6.2 Hz, 1 H), 4.10–4.05 (m, 1 H), 1.27 (d, $J = 6.3$ Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.91, 166.11, 158.09, 152.93, 137.97, 133.46, 130.69, 129.87, 129.85, 128.60, 127.22, 121.98, 111.67, 94.42, 71.24, 65.48, 62.24, 18.11. HRMS (ESI^+): *m/z* calcd. for $C_{19}H_{18}O_6Na$ $[M+Na]^+$ 365.1001, found 365.1002.

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