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Palladium-catalyzed electrochemical C(sp³)−H acetoxylation of alcohol derivatives with an *exo*-directing group†

Daisuke Ogawa,[a] Ayumu Sasaki,[a] Takuya Kochi [ID][a] and Fumitoshi Kakiuchi [ID] *[a,b]

Palladium-catalyzed electrochemical C(sp³)−H acetoxylation to prepare 1,2-diol derivatives was achieved using oxime ethers as *exo*-directing groups. Various substrates containing alkoxy groups with a methyl branch at the α-position as well as norbornan-2-ol derivative were acetoxylated only using a catalytic amount of Pd(OAc)₂ along with NaOAc/Ac₂O/AcOH under anodic oxidation conditions.

Introduction

Combining metal-catalyzed C–H bond cleavage with electrochemical oxidation has become a widely-used strategy for environmentally-benign organic synthesis, because both technologies can contribute to reducing the amounts of reactive reagents and inevitable by-products.[1,2] One of the challenges in electrochemical reactions, in search of greener synthesis, is avoiding the use of excessive mediators and supporting electrolytes other than the actual substrates directly involved in the transformation. One of the strategies to achieve this goal in metal-catalyzed electrochemical C–H functionalization is to utilize the cheap functionalizing agents that also work as a supporting electrolyte. In this case, the redox process with an electrode may proceed for either the substrate or the metal catalyst. In this context, our group has developed some C–H chlorination and bromination reactions[3] of aromatic compounds using combinations of palladium catalysts with platinum electrodes, and anodic oxidation of halide ions is considered to produce halogen species at high oxidation states (Fig. 1a).[4]

In contrast to the metal-catalyzed electrochemical C–H functionalization of aromatic compounds, far fewer reports have been made on those of unreactive C(sp³)–H bonds.[5–7] For example, Mei and co-workers reported in 2017 on the palladium-catalyzed electrochemical C(sp³)–H oxidation to introduce oxygen functionalities at the β-position of the imine carbon.[5] In this reaction, β-hydroxy imine derivatives were obtained as products, and the reaction was considered to
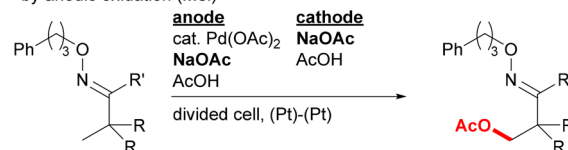
proceed *via* direct anodic oxidation of electron-rich palladium complexes formed by chelation-assisted C–H bond cleavage (Fig. 1b). Sanford's group also reported on a similar oxime-
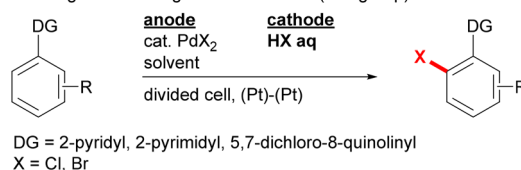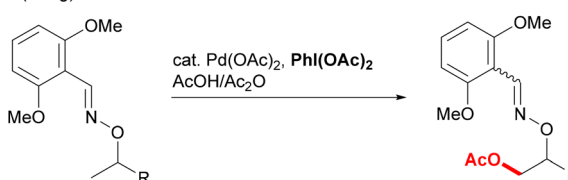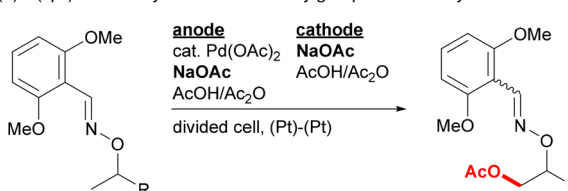

Fig. 1 Palladium-catalyzed C−H oxidative functionalizations.

[a]*Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan. E-mail: kakiuchi@chem.keio.ac.jp*
[b]*JST, CREST, 4-1-8 Honcho, Kawaguchi, Saitama, 332-0012, Japan*
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directed β-oxygenation of the imine carbon as well as benzylic C–H oxidation using several nitrogen directing groups.[6] Inspired by these examples, we envisioned that the use of the metal-catalyzed electrochemical C–H functionalization technique for Dong's system reported in 2012,[8] in which oxime ethers were used as *exo*-directing groups (Fig. 1c), would provide an efficient method for synthesis of 1,2-diol derivatives.

Here we report the palladium-catalyzed electrochemical C(sp³)–H acetoxylation to prepare 1,2-diol derivatives using oxime ethers as *exo*-directing groups (Fig. 1d). Various substrates containing alkoxy groups with a methyl branch at the α-position were acetoxylated at the methyl group only using a catalytic amount of Pd(OAc)₂ along with NaOAc/Ac₂O/AcOH under anodic oxidation conditions. Acetoxylation at a methine carbon was also possible for a norbornan-2-ol derivative.

Results and discussion

The optimized reaction conditions for the reaction of oxime ether **1a** to form acetoxylation product **2a** are as follows (Table 1): the reaction was conducted using an H-type divided cell equipped with two platinum electrodes, and two chambers were separated by a cation exchange membrane, Neosepta CSE. While substrate **1a** and 10 mol% of Pd(OAc)₂ was added to the anodic chamber, NaOAc, used as both an electrolyte and a substrate, and a 50 : 1 mixture of AcOH and Ac₂O was introduced to both chambers. The reaction was conducted with a 1.0 mA constant current at 90 °C for 21 h. For the optimization of the reaction conditions, the yield of product **2a** was determined by adding the NMR yield of the (*E*)-isomer with the yield of (*Z*)-isomer calculated based on the GC ratio of the (*E*)/(*Z*)-isomers. Under the optimized reaction conditions, product **2a** was formed in 72% yield with an (*E*)/(*Z*)-ratio of 3.0 (entry 1). Some byproducts, such as 2,6-dimethoxybenzaldehyde and -benzonitrile, were structurally determined, but no oxidation was observed at the 3- or 4-position of the 2-butoxy group. Reducing the amount of Pd(OAc)₂ to 5.0 mol% decreased the yield to 38% (entry 2). Substrate **1a** contains a 2,6-dimethoxyphenyl group in the directing group. While the use of 2,4,6-trimethoxyphenyl group (**1b**) provided the corresponding product **2b** in a similar yield (entry 3), the substrate containing a 2,6-dimethoxy-4-trifluoromethylphenyl (**1c**) or a 2,6-dichlorophenyl (**1d**) group gave the corresponding product in a lower yield (entries 4 and 5). Extension of the reaction time to 24 h also reduced the yield, probably due to decomposition of the product (entry 6). With keeping the same electronic equivalent at 2.0 F mol⁻¹, the electric current value was varied, but the reactions at 0.5 mA (43 h) and 1.5 mA (14 h) gave **2a** in lower yields (entries 7 and 8). Several cation exchange membranes, such as Nafion 117, 324, and 966, and a sand core were also examined but provided product **2a** in lower yields (entries 9–12). When AcOH was used as a sole solvent instead of AcOH/Ac₂O (50 : 1 v/v), the yield slightly lowered to 60% (entry 13), probably because Ac₂O promotes

Table 1 Optimization of reactions conditions[a]

Entry	Variation from optimized conditions	Yield[b] (%)	E/Z[c]
1	None	72 (64)[d]	3.0/1 (3.9/1)[d]
2	5 mol% of Pd(OAc)₂	38	4.0/1
3	DG_b instead of DG_a [**1b**]	72 [**2b**]	3.6/1
4	DG_c instead of DG_a [**1c**]	47 [**2c**]	3.8/1
5	DG_d instead of DG_a [**1d**]	33 [**2d**]	0.6/1
6	24 h, 2.2 F/mol	64	3.8/1
7	0.5 mA, 43 h (2.0 F mol⁻¹)	61	3.3/1
8	1.5 mA, 14 h (2.0 F mol⁻¹)	59	3.2/1
9[e]	Nafion 117 instead of Neosepta CSE	51	4.5/1
10[e]	Nafion 324 instead of Neosepta CSE	52	4.3/1
11[e]	Nafion 966 instead of Neosepta CSE	49	4.4/1
12	Sand core instead of Neosepta CSE	53	4.1/1
13	AcOH only instead of AcOH/Ac₂O (50 : 1 v/v)	60	4.1/1
14	Without Pd(OAc)₂	nd	—
15	Without electric current	2	2.7/1
16	Undivided cell	35	3.8/1

[a] Reaction conditions: **1a** (0.4 mmol, anode), Pd(OAc)₂ (0.04 mmol, anode), NaOAc (3.2 mmol each, both chambers), AcOH/Ac₂O (50 : 1 v/v, 4 mL each, both chambers), an H-type divided cell with two platinum electrodes and a Neosepta CSE membrane, 90 °C, 1.0 mA, 21 h, 2.0 F mol⁻¹. [b] Combined yields of (*E*)- and (*Z*)-isomers calculated based on the NMR yield of (*E*)-isomer and the GC ratio of (*E*)/(*Z*)-isomers. [c] GC ratios of (*E*)/(*Z*)-isomers. [d] Numbers in parentheses are the yield and the (*E*)/(*Z*)-ratio of the isolated product. [e] 1.5 mA, 14 h (2.0 F mol⁻¹).

the regeneration of Pd(OAc)₂ with avoiding catalyst decomposition.[9] The desired reaction did not proceed without using Pd (OAc)₂ or an electric current (entries 14 and 15). The use of an undivided cell instead of a divided cell reduced the product yield to 35%, and a black deposit, presumed to be palladium black, was observed on the cathode (entry 16). Under the reaction conditions for entry 1, product **2a** was isolated in 64% yield (entry 1).

Substrate scope was examined by incorporating various types of alkoxy groups onto the nitrogen atom of the 2,6-dimethoxybenzylideneamino group and by isolating the products (Fig. 2). Various substrates containing α-branched ethoxy groups were first investigated. The reaction of substrate **1e** bearing 1-pentyl group proceeded to afford the corresponding product **2e** in 51% yield. For the reaction of methyl-substituted substrate **1f**, monoacetoxylation product **2f** was obtained in 59% yield, while only a trace amount of the corresponding diacetoxylation product was detected by GCMS analysis. Substrates
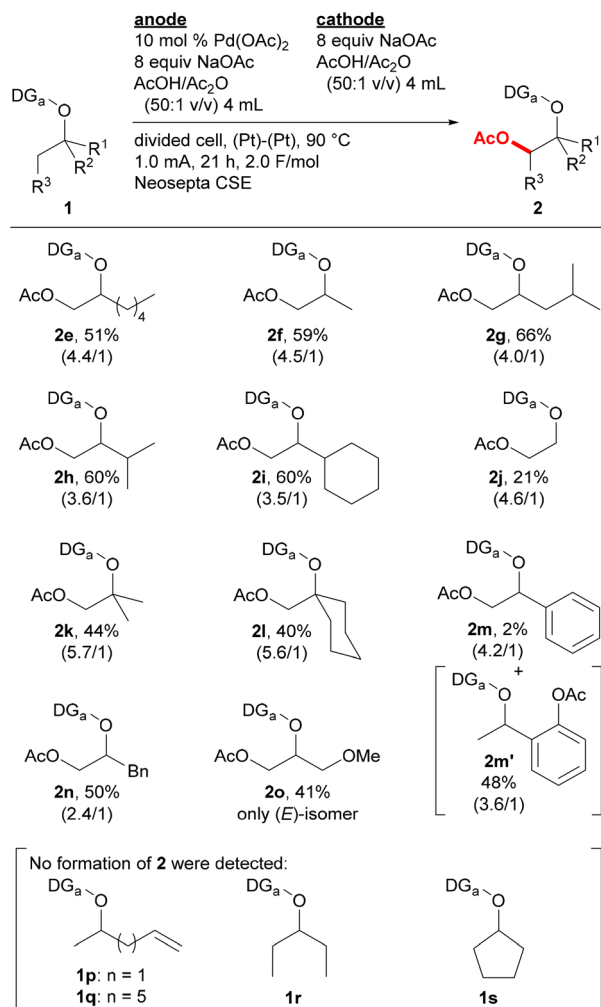
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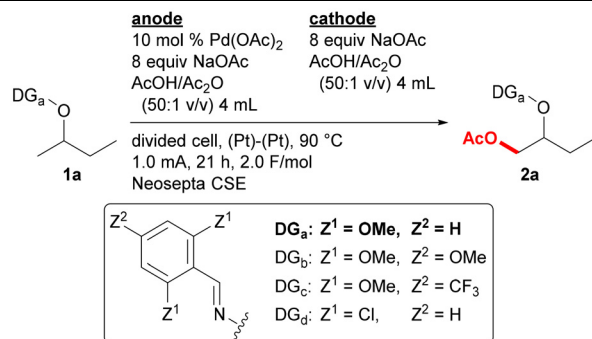
Fig. 2 Substrate scope. Reaction conditions: **1** (0.4 mmol, anode), Pd(OAc)$_2$ (0.04 mmol, anode), NaOAc (3.2 mmol each, both chambers), AcOH/AC$_2$O (50 : 1 v/v, 4 mL each, both chambers), an H-type divided cell with two platinum electrodes and a Neosepta CSE membrane, 90 °C, 1.0 mA, 21 h, 2.0 F mol^{-1}. Isolated yields are presented, and E/Z ratios are shown in parentheses.
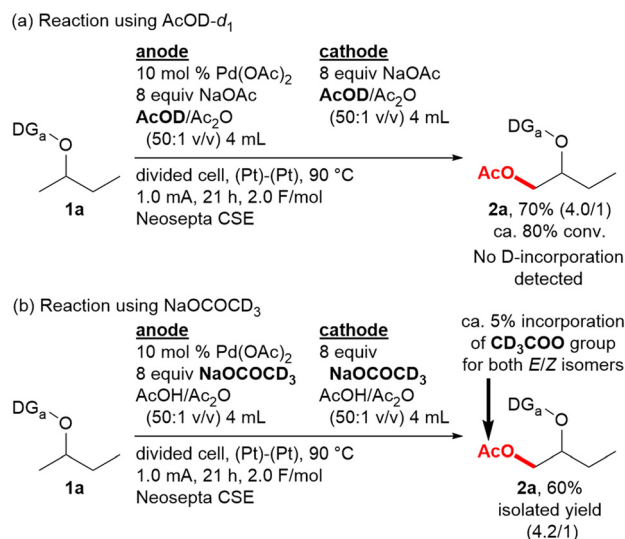
bearing branched alkyl groups such as isobutyl (**1g**), isopropyl (**1h**), and cyclohexyl (**1i**) groups at the α-position were also monoacetoxylated to provide products **2g**–**2i** in 60–66% yields. While only 21% yield of product **2j** was obtained by the reaction of a substrate with no branch at the α-position (**1j**), the reaction of substrates with α,α-dibranched ethoxy group such as *tert*-butoxy (**1k**) and 1-methylcyclohexyloxy (**1l**) groups gave monoacetoxylation products **2k** and **2l** in 44 and 40% yields, respectively. While the reaction of a substrate with a phenyl group at the α-position (**1m**) mostly provided C(sp^2)–H acetoxylation product **2m′** with only a small amount of the desired C(sp^3)–H acetoxylation product **2m**, benzyl-substituted substrate **1n** was selectively converted to C(sp^3)–H acetoxylation product **2n** in 50% yield. Substrates having a functional group were also examined. The reaction of substrate **1o** bearing a 1-methoxypropan-2-yl group offered glycerine derivative **2o**

with three different protecting groups in 41% yield, acetoxylation products were not detected for the reaction of substrates containing an alkene moiety (**1p** and **1q**). The reaction of substrate without a methyl substituent on the α-carbon of the alkoxy group is much more challenging, and no acetoxylation product was obtained for the reaction of substrates derived from 3-pentyl and cyclopentyl alcohols (**1r** and **1s**, respectively). However, the acetoxylation of a mixture of *endo/exo*-norbornan-2-ol derivative (**1t**) proceeded at the 1-position to give the corresponding product **2t** in 30% yield as a mixture of stereoisomers (Scheme 1).

In order to gain an understanding of the mechanism, the reaction of **1a** was conducted in AcOD (Scheme 2a). The yield, determined in the same way as those in Table 1, was comparable to the reaction in AcOH (Table 1, entry 1), and no deuterium incorporation was detected for either product **2a** or recovered **1a** by ^{2}H NMR. Therefore, the C–H bond cleavage by the concerted metalation-deprotonation (CMD) mechanism is considered to be irreversible in this case. The reaction using NaOCOCD$_3$ was also conducted, and ^{1}H NMR analysis suggested that the amount of the product possessing a CD$_3$COO group instead of an AcO group in the isolated product **2a** is *ca.* 5%, which is nearly equal to the proportion
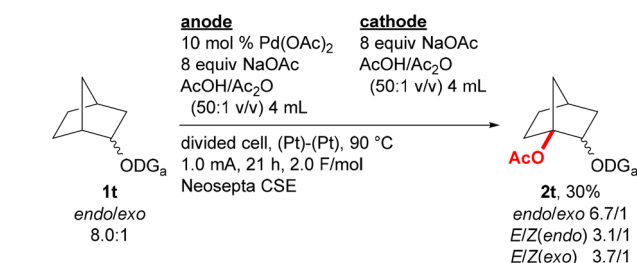
Scheme 1 Reaction of norbornan-2-ol derivative **1t**.

Scheme 2 Deuterium-labelling experiments.

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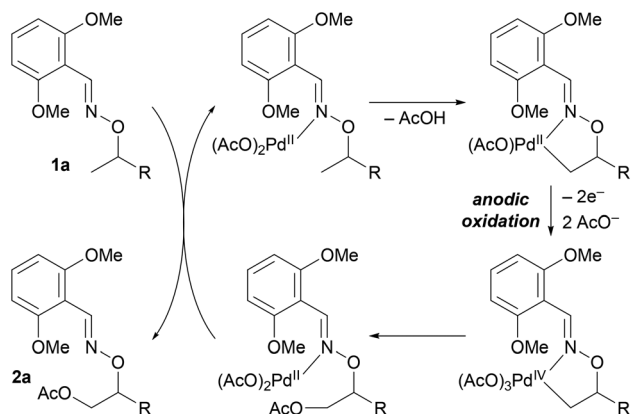This journal is © The Royal Society of Chemistry 2024

Fig. 3 A proposed catalytic cycle.

of the CD_3CO group in the total amount of the acetyl group in the reaction system (Scheme 2b). Therefore, the acetate ion in the NaOAc should be rapidly exchanged with AcOH during the reaction.

A proposed catalytic cycle of this reaction is described in Fig. 3, though the exact number of acetates on the palladium center would be highly speculative. Substrate coordination to the palladium center, followed by C–H bond cleavage *via* a CMD mechanism, gives a palladium(II) metallacycle species. Anodic oxidation of the palladium complex then occurs to provide a high-oxidation-state palladium species, which undergoes rapid reductive elimination to form a C–O bond. Ligand exchange with **1a** provides product **2a**.

Conclusions

Palladium-catalyzed electrochemical C(sp³)–H acetoxylation of alcohol derivatives was achieved using an oxime as an *exo*-directing group to prepare 1,2-diol derivatives. Various substrates containing alkoxy groups with a methyl branch at the α-position were acetoxylated at the methyl group only using Pd(OAc)₂ catalyst and NaOAc in Ac₂O/AcOH under anodic oxidation conditions. The acetoxylation of a norbornan-2-ol derivative also proceeded at the 1-position.

Experimental

A general procedure for the palladium-catalyzed electrochemical acetoxylation

The electrochemical oxidation was carried out in an H-type divided cell equipped with two platinum electrodes (1.7 × 1.7 cm²) and a cation-exchange membrane. The anodic chamber was charged with a solution of oxime ether **1** (0.4 mmol, 1 equiv.), NaOAc (262.5 mg, 3.2 mmol, 8 equiv.), and palladium acetate (8.98 mg, 0.04 mmol, 10 mol%) in AcOH/Ac₂O (4 mL, 50:1 v/v). The cathodic chamber was charged with a solution of NaOAc (262.5 mg, 3.2 mmol, 8 equiv.) in AcOH/Ac₂O (4 mL, 50:1 v/v). After the mixture in the anodic chamber was stirred for 15 min at 90 °C, an electric field was applied at room temperature under a 1.0 mA constant current condition for 21 h. After the reaction, the mixtures in both of the chambers were transferred to a flask through a funnel. The electrodes and H-type divided cell were washed with AcOEt. The mixture was mixed with an aqueous solution of NaHCO₃ and was extracted with AcOEt. The combined organic portions were washed with brine. The resulting solution was dried over MgSO₄ and concentrated. The acetoxylation product **2** was isolated by flash column chromatography. The *E/Z* ratios of the products were determined based on the integral ratios of the ¹H NMR signals corresponding to the acetyl group.

Acetoxylation product 2a. *E/Z* = 3.9/1. The general procedure was followed 94.6 mg (0.40 mmol) of **1a**. Silica gel chromatography (hexane/EtOAc 5:1) of the crude material afforded **2a** in 64% yield (75.6 mg, 0.26 mmol) as a colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

Acetoxylation product 2e. *E/Z* = 4.4/1. The general procedure was followed 111 mg (0.40 mmol) of **1e**. Silica gel chromatography (hexane/EtOAc 5:1) of the crude material afforded **2e** in 51% yield (69.0 mg, 0.20 mmol) as a colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

Acetoxylation product 2f. *E/Z* = 4.5/1. The general procedure was followed 88.7 mg (0.40 mmol) of **1f**. NH silica gel chromatography (gradient elution: 100% hexane to hexane/EtOAc 5:1) of the crude material afforded **2f** in 59% yield (66.2 mg, 0.24 mmol) as a colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

Acetoxylation product 2g. *E/Z* = 4.0/1. The general procedure was followed 106 mg (0.40 mmol) of **1g**. Silica gel chromatography (hexane/EtOAc 5:1) of the crude material afforded **2g** in 66% yield (85.3 mg, 0.26 mmol) as a colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

Acetoxylation product 2h. *E/Z* = 3.6/1. The general procedure was followed 100 mg (0.40 mmol) of **1h**. Silica gel chromatography (hexane/EtOAc 5:1) of the crude material afforded **2h** in 60% yield (74.2 mg, 0.24 mmol) as a colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

Acetoxylation product 2i. *E/Z* = 3.5/1. The general procedure was followed 116.8 mg (0.40 mmol) of **1i**. Silica gel chromatography (hexane/EtOAc 10:1) of the crude material afforded **2i** in 60% yield (84.1 mg, 0.24 mmol) as a colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

Acetoxylation product 2k. *E/Z* = 5.7/1. The general procedure was followed 94.4 mg (0.40 mmol) of **1k**. Silica gel chromatography (hexane/EtOAc 5:1) of the crude material afforded **2k** in 44% yield (52.0 mg, 0.18 mmol) as a colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

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Acetoxylation product 2l. E/Z = 5.6/1. The general procedure was followed 111.5 mg (0.40 mmol) of **1l**. Silica gel chromatography (hexane/EtOAc 7 : 1) of the crude material afforded **2l** in 40% yield (54.5 mg, 0.16 mmol) as a colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

Acetoxylation products 2m and 2m′. E/Z(**2m**) = 4.2/1. E/Z(**2m′**) = 3.6/1. The general procedure was followed 115.6 mg (0.41 mmol) of **1m**. Silica gel chromatography (hexane/EtOAc 3 : 1) of the crude material afforded **2m** and **2m′** in 50% combined yield (70.2 mg, 0.20 mmol, **2m** : **2m′** = 1 : 20) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): [**2m′**] **Major isomer** δ 8.45 (s, 1H), 7.54–7.53 (m, 1H), 7.32–7.29 (m, 1H), 7.27–7.25 (m, 1H), 7.27–7.21 (m, 2H), 7.08–7.05 (m, 1H), 6.54 (d, J = 6.8 Hz, 2H), 5.55 (q, J = 6.6 Hz, 1H), 3.79 (s, 6H), 2.32 (s, 3H), 1.59 (d, J = 6.3 Hz, 3H). **Minor isomer** (*distinct resonances) δ 6.54 (d, J = 8.6 Hz, 1H), 5.44 (q, J = 6.6 Hz, 1H), 3.80 (s, 6H), 2.24 (s, 3H), 1.44 (d, J = 6.3 Hz, 3H); the analytical data for **2m′** are in good agreement with those reported in literature.[10]

Acetoxylation product 2n. E/Z = 2.4/1. The general procedure was followed with 119.8 mg (0.40 mmol) of **1n**. Silica gel chromatography (hexane/EtOAc 4 : 1) of the crude material afforded **2n** in 50% yield (71.6 mg, 0.20 mmol) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): **Major isomer** δ 8.48 (s, 1H), 7.31–7.12 (m, 6H), 6.57 (d, J = 8.7 Hz, 2H), 4.70–4.64 (m, 1H), 4.29 (dd, J = 11.5, 4.1 Hz, 1H), 4.19 (dd, J = 11.5, 5.4 Hz, 1H), 3.85 (s, 6H), 3.18 (dd, J = 14.2, 5.9 Hz, 1H), 2.98 (dd, J = 14.2, 7.3 Hz, 1H), 2.08 (s, 3H). **Minor isomer** δ 7.47 (s, 1H), 7.31–7.12 (m, 6H), 6.54 (d, J = 8.3 Hz, 2H), 4.63–4.57 (m, 1H), 4.17 (dd, J = 11.5, 5.4 Hz, 1H), 4.11 (dd, J = 11.5, 5.0 Hz, 1H), 3.75 (s, 6H), 3.04 (dd, J = 13.9, 6.3 Hz, 1H), 2.88 (dd, J = 13.9, 6.8 Hz, 1H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): **Major isomer** δ 171.0, 159.0, 144.8, 137.6, 130.9, 129.5, 128.4, 126.3, 109.4, 104.1, 80.8, 64.4, 56.0, 37.0, 20.9. **Minor isomer** δ 170.8, 157.8, 144.3, 137.5, 130.5, 129.6, 128.2, 126.2, 109.4, 103.5, 80.9, 64.4, 55.6, 37.1, 20.9; IR (NaCl, mixed isomers): 3087 w, 3062 w, 3026 w, 3005 w, 2940 m, 2839 w, 1739 s, 1595 s, 1471 s, 1432 m, 1367 w, 1305 w, 1282 w, 1256 s, 1113 s, 1039 m, 944 m, 895 w, 778 m, 748 w, 734 w, 702 m; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for C$_{20}$H$_{23}$NO$_5$Na$^+$ 380.1468, found 380.1472.

Acetoxylation product 2o. The general procedure was followed with 105.7 mg (0.42 mmol) of **1o**. Silica gel chromatography (hexane/EtOAc 3 : 1) of the crude material afforded **2o** in 41% yield (53.4 mg, 0.17 mmol) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.50 (s, 1H), 7.27 (t, J = 8.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 2H), 4.61–4.56 (m, 1H), 4.42–4.33 (m, 2H), 3.84 (s, 6H), 3.72–3.65 (m, 2H), 3.41 (s, 3H), 2.09 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 171.0, 159.1, 145.2, 131.0, 109.2, 104.1, 79.2, 71.2, 63.3, 59.4, 56.0, 20.1; IR (NaCl, mixed isomers): 2938 w, 2840 w, 1740 s, 1596 m, 1471 s, 1434 m, 1368 w, 1344 w, 1307 w, 1257 s, 1208 m, 1114 s, 1045 m, 956 m, 881 w, 779 m, 731 w, 633 w; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for C$_{15}$H$_{21}$NNaO$_6^+$ 334.1261, found 334.1263.

Acetoxylation product 2t. $endo/exo$ = 6.7/1, E/Z($endo$) 3.1/1, E/Z(exo) 3.7/1. The general procedure was followed 108.6 mg

(0.39 mmol) of **1t**. Silica gel chromatography (hexane/EtOAc 5 : 1) of the crude material afforded **2t** in 30% yield (39.3 mg, 0.12 mmol) as colorless oil. The analytical data for this product are in good agreement with those reported in literature.[8]

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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