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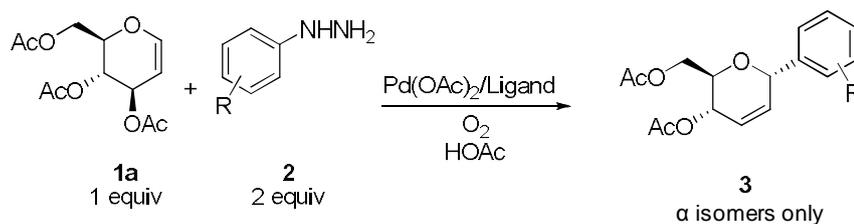
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Oxidative Heck Reaction of Glycals and Aryl Hydrazines: A Palladium-Catalyzed C -Glycosylation

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Abstract: An efficient Heck type C -glycosylation of glycals *via* the C-N bond cleavage of aryl hydrazines has been developed. The flexibility of the reaction was tested by the substrate scope, consisting of glycals from different carbohydrate origins as well as aryl hydrazines with various substituents. Pure α - C -glycosides were obtained when 3*R* glycals were employed while α , β mixtures were observed with 3*S* glycals.

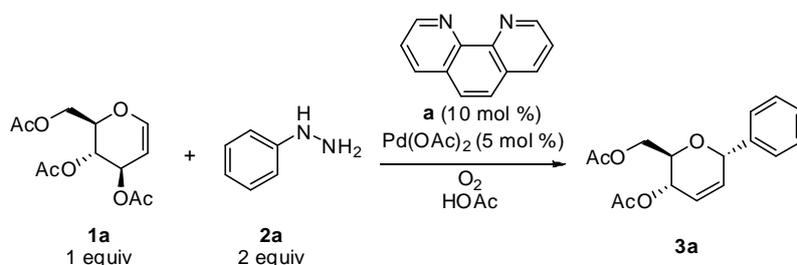
Aryl- C -glycosides are a group of compounds possessing aryl groups as the aglycon at the anomeric carbon position. Many synthetic methods have been discovered since 1980s towards aryl- C -glycosides due to their frequent presence in natural products¹ and their

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6 important biological functions such as enzyme inhibitors and sugar mimics.² Until now,
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8 most of the synthetic methods have focused on the transition metal catalyzed cross
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10 coupling reaction to construct the glycosidic C-C bond. Earlier strategies comprise using
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12 pre-activated reagents either on the glycal parts such as iodinated or stannylated glycals³
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14 or on the aromatic parts such as organometallic reagents.⁴ Therefore, problems that often
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16 arise from early methods include restricted substrate scopes and high toxicity. In the last
17
18 decade, Heck reactions were employed to the syntheses of aryl-*C*-glycosides by direct
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20 coupling of inactivated glycals and aromatic compounds such as aryl halides,⁵ aryl
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22 boronic acids⁶ and benzoic acids.⁷ Since the reagents in these reactions are moisture
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24 stable and relatively environmental friendly, Heck reaction became one of the most
25
26 attractive approach to aryl-*C*- glycosylation. There are two main classes of products
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28 generated by Heck type aryl-*C*-glycosylation. One is the 2,3-deoxy-*C*-glycosides, which
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30 is generated *via* beta-heteroatom elimination when the glycals are protected by good
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32 leaving groups such as acetyl group. The other is the 2-deoxy-*C*-glycosides, which will
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34 undergo beta-hydride elimination when the glycals are protected by poor leaving groups
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36 such as silyl or benzyl groups.
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44 Recently, C-C bond constructions *via* cleavage of pre-activated C-N bond have attracted
45
46 considerable attention.⁸ Inspired by the versatility of the C-N bond activation, we
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48 envisioned that we could further explore the synthetic methods⁹ towards aryl-*C*-glycoside
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50 by coupling glycals with activated anilines. The general approaches to activate aniline C-
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52 N bonds include conversion to diazonium salts or hydrazines. We decided to make
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54 hydrazines as the coupling partners of glycals for two main reasons. Firstly some of the
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56 diazonium salts such as diazonium halides are highly explosive and the stable diazonium
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salts such as diazonium tetrafluoroborates or hexafluorophosphates are prone to decompose upon heating¹⁰ while heating is usually an indispensable condition for transition metal catalyzed coupling reaction. The other reason accounting for our choice is that aryl hydrazines are much more commercially available than aryl diazonium salts. As a result, we herein describe our results for the syntheses of aryl-*C*-glycosides by a palladium catalyzed cross coupling reactions of glycals and aryl hydrazines.¹¹

Table 1. Palladium-catalyzed Ferrier type *C*-glycosylation with 3,4,6-tri-*O*-acetyl glucal and phenyl hydrazine.^a



entry	ligand	solvent	time (h)	temp (°C)	yield (%) ^b
1	-	DCE	24	40	-
2	-	DCE	12	80	43
3	-	PhCl	12	80	40
4	-	PhCl	8	80	55
5 ^c	-	AcOH/PhCl	8	80	71
6	a	AcOH	6	80	82
7	a	AcOH	6	50	35
8	a	AcOH	6	60	77
9	a	AcOH	6	65	90

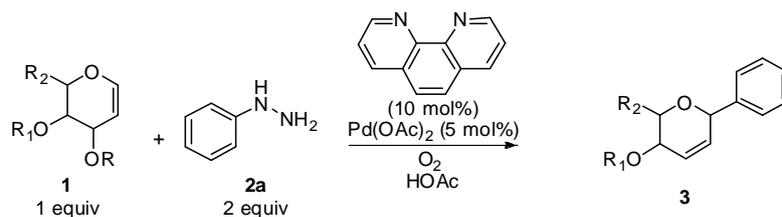
^aUnless otherwise specified, reactions were carried out with 1 equivalent of **1a**, 2 equivalents of **2a**, 5% catalyst, 10% ligand and 1 atm of oxygen. ^b Isolated yield. ^c PhCl : AcOH (v/v) = 1:1

Our initial effort was made to achieve the successful coupling of commercially available 3, 4, 6-tri-*O*-acetyl-D-glucal with phenyl hydrazine. The reaction was carried out by the catalysis of palladium acetate at 40 °C under 1 atm oxygen (entry 1, Table 1) in

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6 dichloroethane. No new compound was detected after 12 hours stirring. Fortunately,
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8 increasing the reaction temperature to 80 °C (entry 2, Table 1) with other factors
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10 remaining unchanged offered the desired product **3a** in 43% yield as pure α isomer.
11
12 Several commonly used organic solvent such as chlorobenzene (entry 3-5, Table 1) and
13
14 acetic acid (entry 5-6, Table 1) were tested and it was proven that higher yield was
15
16 obtained by using acetic acid as solvent. Addition of 1,10-phenanthroline (entry 6, Table
17
18 1) as ligand was found to further enhance the yield. Screening the reaction at different
19
20 temperatures (entry 7-9, Table 1) revealed that 65 °C was optimal to give the desired
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22 product in highest yield (90%) as pure α form.
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28 With these optimized conditions in hand, we first explored the substrate scope of glycols
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30 and the results were summarized in Table 2. Glycols with different protecting groups
31
32 were tested and the results show that the desired products were found only when the C-3
33
34 protecting groups of glycols are acetyl (**3a** - **3e**) or ethoxycarbonyloxyl (**3f**). Possibly the
35
36 acetic acid as solvent restricts the reactivity of glycols with other protecting groups. Other
37
38 leaving groups such as benzoyl, pivaloyl or *tert*-butoxycarbonyloxy were proven to be
39
40 inactive under the standard conditions. Subsequently, we moved on to investigate the
41
42 reactivities of glycols prepared with different carbohydrate origins. Results revealed that
43
44 glycols prepared from galactose (**3b**), L-6-deoxyglucose (**3d**) and ribose (**3c**) also reacted
45
46 well with phenyl hydrazine to provide the corresponding *C*-glycosides in moderate to
47
48 high yields.
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54 **Table 2.** *C*-Glycosylation coupling reaction of glycols and phenyl hydrazine. ^{a, b}
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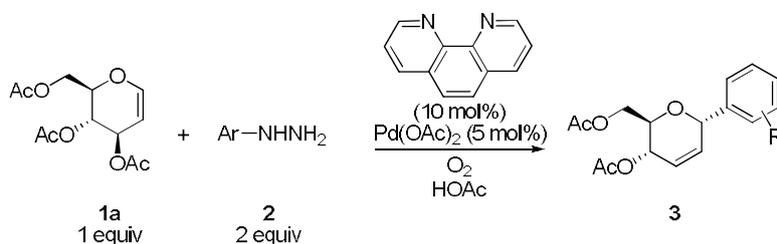
entry	glycal	product	yield (%)
1			90
2			85
3			81
4			83
5			72
6			43

^aReactions were carried out with 1 equivalent of **1a**, 2 equivalents of **2a**, 5% catalyst, 10% ligand and 1 atm of oxygen at 65 °C for 6 hours. ^b Isolated yield

Next, 3,4,6-tri-*O*-acetylglucal was treated with various hydrazines of different substituents on different positions (Table 3). Notably, if phenyl hydrazine was replaced with the corresponding hydrochloric salt, no desired product was detected after 48 hours. Among all the hydrazines tested, *ortho*-substituted aryl hydrazines were found to have

the worst reactivities. Only *o*-chlorophenylhydrazine could offer the corresponding aryl-*C*-glycoside in moderate yield (**3i**). Other *ortho*-substituted aryl hydrazines such as *o*-tolylphenylhydrazine or *o*-bromophenylhydrazine failed to offer any desired product. It is possible that the more steric hindered bromo or methyl group in *ortho* position prevents the aryl-palladium complex from approaching the glycal and thus the migratory insertion is inhibited.¹² Moderate to good yields were obtained from various *meta*- (**3g**, **3m**) or *para*-phenylhydrazines (**3h**, **3j**, **3k**, **3l**, **3n**). No desired product was detected for aryl hydrazines with strong electron donating groups, such as methoxyl or ethoxyl due to the possible decomposition of hydrazine substrates under standard conditions such as 1 atm oxygen and high temperature. All the aryl-*C*-glycosides were obtained in pure α selectivity.

Table 3. *C*-Glycosylation coupling reaction of 3,4,6-tri-*O*-acetylglucal and various aryl hydrazines.^{a, b}

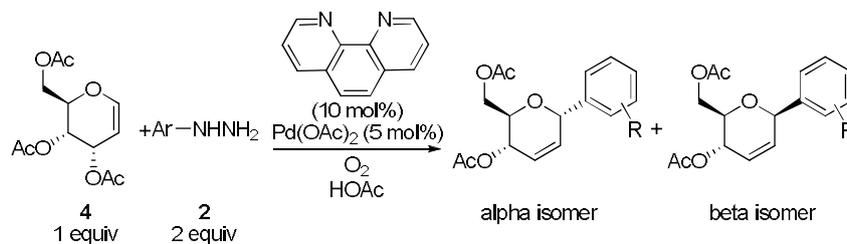


entry	R	time (h)	yield (%)
1	3-Me-C ₆ H ₄ (3g)	4	80
2	4-Me-C ₆ H ₄ (3h)	3	86
3	2-Cl-C ₆ H ₄ (3i)	8	43
4	4-Br-C ₆ H ₄ (3j)	6	85
5	4-COOMe-C ₆ H ₄ (3k)	10	51
6	4-I-C ₆ H ₄ (3l)	2	30
7	3, 5-CF ₃ -C ₆ H ₃ (3m)	8	64
8	4-F-C ₆ H ₄ (3n)	4	79

^aUnless otherwise specified, reactions were carried out with 1 equiv-alent of **1a**, 2 equivalents of **2**, 5% catalyst, 10% ligand and 1 atm of oxygen at 65 °C. ^b Isolated yield

Although all the reported transition metal catalyzed Heck type *C*-glycosylation methods showed α selectivity, few reports provided the reason. The stereoselectivity could be attributed to any of the 3 pre-existing chiral centers on the glycal substrates. In 2009, Ye's group deduced that the stereochemistry of C3 on glycal was the main reason for α selectivity.^{5b} Due to the steric hindrance between the bulky palladium species and the protecting group on C3, the palladium species can only approach glycals from the side opposite to the C3 group. Thus, α product was obtained exclusively. To test this hypothesis and prepare β aryl-*C*-glycosides, (3*S*, 4*S*, 6*R*)-tri-*O*-acetylglycal was synthesized¹³ and treated with various hydrazines under standard conditions. The results were summarized in Table 4. Instead of pure α product, a mixture of α and β isomers were obtained, with ratios ranging from 1:1 to 1:0.6. These results suggest that the stereochemistry at C-3 is not the only determining factor for the observed α selectivity.

Table 4. *C*-Glycosylation coupling reaction of (3*S*, 4*S*, 6*R*)-tri-*O*-acetylglycal and various aryl hydrazines.^{a, b}



entry	R	time (h)	yield (h)	α : β
1	Ph (3o)	6	79	1:1
2	4-F-C ₆ H ₄ (3p)	4	75	1:0.81
3	4-Br-C ₆ H ₄ (3q)	6	83	1:0.6
4	3-Me-C ₆ H ₄ (3r)	4	74	1:0.87

^a Unless otherwise specified, reactions were carried out with 1 equivalent of **4**, 2 equivalents of **2**, 5% catalyst, 10% ligand and 1 atm of oxygen at 65 °C. ^b Isolated yield.

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6 In conclusion, an efficient Heck type C-glycosylation method of glycols and aryl
7 hydrazines, by the C-N bond cleavage, has been developed. The substrate scope includes
8 glycols with protecting groups which function as good leaving groups and various aryl
9 hydrazines. High stereoselectivities were achieved when 3*R* glycols substrate were used.
10
11 On the contrary, α and β mixtures were obtained when 3*S* glycols were chosen. To the
12 best of our knowledge, this is the first example for the formation of β aryl- C-glycoside
13 *via* Heck type reaction. Since aryl hydrazines could be prepared by short steps from their
14 corresponding anilines,¹⁴ this protocol presents promising applications to the syntheses
15 of aryl-C-glycosides containing natural products.
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28 Experimental Section

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30 **General procedure of Pd catalyzed cross-coupling of glycols and aryl hydrazines:** To
31 a round bottom flask containing the solution of glycol (1 equiv), palladium(II) diacetate
32 (5% mol) and 1, 10-phenantroline (10% mol) in acetic acid (2.5 mL/mmol) at 65 °C,
33 phenyl hydrazine (1.5 equiv) in acetic acid (5 mL/mmol) was added dropwise. The
34 mixture was allowed to stir at 65 °C for the indicated time in Scheme 1, Table 2 and
35 Table 3. Then the mixture was diluted with ethyl acetate (20 mL/mmol), filtered, washed
36 with water (5 mL/mmol) and brine (5 mL/mmol). The organic layer was evaporated and
37 the residue was purified by flash column chromatography to afford the product.
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50 **((2*R*,3*S*,6*S*)-3-Acetoxy-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3a).**

51 Following the general procedure, the crude product was purified over a silica gel column
52 using hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 52 mg, 90% yield: ¹H
53 NMR (CDCl₃, 400 MHz) δ 2.07 (s, 3H), 2.09 (s, 3H), 3.83–3.97 (m, 1H), 4.09 (dd, *J* =
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6 3.1, 12.0 Hz, 1H), 4.25 (dd, $J = 5.9, 12$ Hz, 1H), 5.29–5.33 (m, 2H), 5.97–6.01 (m, 1H),
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8 6.19 (ddd, $J = 1.5, 3.0, 10.4$ Hz, 1H), 7.32–7.39 (m, 5H); ^{13}C NMR (CDCl_3 , 400 MHz) δ
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10 20.8, 21.1, 62.9, 65.0, 69.3, 73.7, 125.0, 127.9, 128.3, 128.5, 131.5, 138.8, 170.5,
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12 170.9; $[\alpha]_{\text{D}}^{20} = 13.9$ (c 2.00, CHCl_3); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{O}_5\text{Na}$
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14 $[\text{M}+\text{Na}]^+ 313.1052$, found 313.1053.
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19 **((2R,3R,6S)-3-Acetoxy-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3b).**

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21 Following the general procedure, the crude product was purified over a silica gel column
22
23 using hexane/EtOAc system (6:1 to 4:1) to give a pale yellow oil, 49 mg, 85% yield: ^1H
24
25 NMR (CDCl_3 , 400 MHz) δ 1.99 (s, 3H), 2.11 (s, 3H), 3.92–3.95 (m, 1H), 4.14–4.23 (m,
26
27 2H), 5.11 (dd, $J = 2.6, 5.1$ Hz, 1H), 5.39–5.41 (m, 1H), 6.20 (ddd, $J = 2.1, 5.2, 10.2$ Hz,
28
29 1H), 6.41 (ddd, $J = 0.5, 3.6, 10.2$ Hz, 1H), 7.30–7.35 (m, 5H); ^{13}C NMR (CDCl_3 , 400
30
31 MHz) δ 20.7, 20.9, 62.8, 63.8, 68.3, 73.8, 123.5, 127.8, 128.2, 128.5, 133.3, 138.3, 170.6,
32
33 170.6; $[\alpha]_{\text{D}}^{20} = -371.1$ (c 3.00, CHCl_3); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{18}\text{O}_5\text{Na}$
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35 $[\text{M}+\text{Na}]^+ 313.1052$, found 313.1060.
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41 **(3S,6R)-6-Phenyl-3,6-dihydro-2H-pyran-3-yl acetate (3c).** Following the general
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43 procedure, the crude product was purified over a silica gel column using hexane/EtOAc
44
45 system (10:1 to 8:1) to give a yellow oil, 35 mg, 81% yield: ^1H NMR (CDCl_3 , 400 MHz)
46
47 δ 2.11 (s, 3H), 3.69 (dd, $J = 5.2, 11.9$ Hz, 1H), 4.04 (dd, $J = 4.4, 11.9$ Hz, 1H), 5.21 (t, J
48
49 $= 2.1$, 1H), 5.22–5.29 (m, 1H), 6.03–6.07 (m, 1H), 6.16 (ddd, $J = 1.2, 2.6, 10.4$ Hz, 1H),
50
51 7.30–7.39 (m, 5H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 21.1, 64.7, 64.7, 75.1, 124.5, 127.8,
52
53 128.3, 128.6, 133.3, 139.1, 170.7; $[\alpha]_{\text{D}}^{20} = 170.0$ (c 3.00, CHCl_3); HRMS (ESI) calcd for
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55 $\text{C}_{13}\text{H}_{14}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+ 241.0841$, found 241.0842.
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6 **(2S,3R,6R)-2-Methyl-6-phenyl-3,6-dihydro-2H-pyran-3-yl acetate (3d)**. Following the
7
8 general procedure, the crude product was purified over a silica gel column using
9
10 hexane/EtOAc system (8:1) to give a bright yellow oil, 38 mg, 83% yield: ¹H NMR
11
12 (CDCl₃, 400 MHz) δ 1.25 (d, *J* = 6.44 Hz, 3H), 2.10 (s, 3H), 3.87 (t, *J* = 6.3 Hz, 1H),
13
14 5.05 (m, 1H), 5.23 (q, *J* = 2.2 Hz, 1H), 5.95 (ddd, *J* = 2.1, 3.2, 10.3 Hz, 1H), 6.13 (ddd, *J*
15
16 = 1.4, 2.8, 10.3 Hz, 1H), 7.30 – 7.42 (m, 5H); ¹³C NMR (CDCl₃, 400 MHz) δ 17.3, 21.2,
17
18 68.0, 69.8, 72.8, 124.2, 127.9, 128.1, 128.5, 132.2, 139.6, 170.8; [α]_D²⁰ = -34.8 (*c* 1.50,
19
20 CHCl₃); HRMS (ESI) calcd for C₁₄H₁₆O₃Na [M+Na]⁺ 255.0997, found 255.0989.
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26 **(2R,3R,6S)-3-(Benzyloxy)-2-((benzyloxy)methyl)-6-phenyl-3,6-dihydro-2H-pyran**

27
28 **(3e)**. Following the general procedure, the crude product was purified over a silica gel
29
30 column using hexane/EtOAc system (10:1 to 6:1) to give a colorless oil, 56 mg, 72%
31
32 yield: ¹H NMR (CDCl₃, 400 MHz) δ 3.60–3.67 (m, 1H), 3.68–3.72 (m, 2H), 4.18–4.21
33
34 (m, 2H), 4.45–4.51 (m, 2H), 4.58–4.64 (m, 2H), 5.32 (d, *J* = 1.5 Hz, 1H), 6.08–6.16 (m,
35
36 2H), 7.25–7.37 (m, 13H), 7.43–7.46 (m, 2H); ¹³C NMR (CDCl₃, 400 MHz) δ 69.2, 70.2,
37
38 70.7, 71.2, 73.3, 74.1, 77.2, 127.2, 127.6, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.4,
39
40 129.6, 138.2, 139.6; [α]_D²⁰ = 22.8 (*c* 1.20, CHCl₃); HRMS (ESI) calcd for C₂₆H₂₆O₃Na
41
42 [M+Na]⁺ 409.1780, found 409.1779.
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49 **((2R,3S,6S)-6-Phenyl-2-((ethoxycarbonyloxy)methyl)-3,6-dihydro-2H-pyran-3-**

50 **yl)methyl ethyl carbonate (3f)**. Following the general procedure, the crude product was
51
52 purified over a silica gel column using hexane/EtOAc system (4:1 to 3:1) to give a brown
53
54 oil, 30 mg, 43% yield: ¹H NMR (CDCl₃, 400 MHz) δ 1.27–1.34 (m, 6H), 3.87–3.91 (m,
55
56 1H), 4.15–4.28 (m, 5H), 4.30–4.33 (m, 1H), 5.21 (dd, *J* = 1.9, 7.6 Hz, 1H), 5.33 (d, *J* =
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6 2.4 Hz, 1H), 6.06 (dt, $J = 2.2, 10.4$ Hz, 1H), 6.20 (ddd, $J = 1.6, 3.1, 10.4$ Hz, 1H), 7.32–
7
8 7.41 (m, 5H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 14.1, 14.1, 64.1, 64.3, 66.0, 68.1, 68.5, 73.7,
9
10 77.0, 124.4, 127.9, 128.1, 128.3, 128.4, 131.7, 138.3, 154.4, 154.9; $[\alpha]_{\text{D}}^{20} = 19.8$ (c 0.80,
11
12 CHCl_3); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{22}\text{O}_7\text{Na}$ $[\text{M}+\text{Na}]^+$ 373.1263, found 373.1263.
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17 **((2R,3S,6S)-3-Acetoxy-6-(m-tolyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3g).**

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19 Following the general procedure, the crude product was purified over a silica gel column
20
21 using hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 49 mg, 80% yield: ^1H
22
23 NMR (CDCl_3 , 400 MHz) δ 2.08 (s, 3H), 2.09 (s, 3H), 2.37 (s, 3H), 3.84–3.88 (m, 1H),
24
25 4.10 (dd, $J = 3.1, 12.0$ Hz, 1H), 4.27 (dd, $J = 5.9, 12$ Hz, 1H), 5.29–5.32 (m, 2H), 5.96–
26
27 6.00 (m, 1H), 6.17–6.20 (m, 1H), 7.13–7.25 (m, 4H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.8,
28
29 21.1, 21.5, 62.9, 65.0, 69.3, 73.7, 124.9, 124.9, 128.4, 128.6, 129.0, 131.6, 138.2, 138.8,
30
31 170.5, 170.9; $[\alpha]_{\text{D}}^{20} = 19.5$ (c 1.50, CHCl_3); HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$
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33 327.1208, found 327.1204.
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39 **((2R,3S,6S)-3-Acetoxy-6-(p-tolyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3h).**

40
41 Following the general procedure, the crude product was purified over a silica gel column
42
43 using hexane/EtOAc system (6:1 to 4:1) to give a pale yellow oil, 52 mg, 86% yield: ^1H
44
45 NMR (CDCl_3 , 400 MHz) δ 2.07 (s, 3H), 2.08 (s, 3H), 2.36 (s, 3H), 3.80–3.84 (m, 1H),
46
47 4.08 (dd, $J = 3.1, 12.0$ Hz, 1H), 4.26 (dd, $J = 5.7, 12.0$ Hz, 1H), 5.30–5.33 (m, 2H), 5.98
48
49 (dt, $J = 2.1, 10.3$ Hz, 1H), 6.17 (ddd, $J = 1.4, 2.9, 10.4$ Hz, 1H), 7.18 (m, 2H), 7.28 (m,
50
51 2H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.8, 21.1, 21.2, 62.9, 65.1, 69.0, 73.7, 125.0, 128.0,
52
53 129.2, 131.6, 135.8, 138.1, 170.5, 170.9; $[\alpha]_{\text{D}}^{20} = 5.2$ (c 1.50, CHCl_3); HRMS (ESI) calcd
54
55 for $\text{C}_{17}\text{H}_{20}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$ 327.1208, found 327.1198.
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((2R,3S,6S)-3-Acetoxy-6-(2-chlorophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate

(3i). Following the general procedure, the crude product was purified over a silica gel column using hexane/EtOAc system (6:1 to 4:1) to give a pale yellow oil, 28 mg, 43% yield: ^1H NMR (CDCl_3 , 400 MHz) δ 2.06 (s, 3H), 2.11 (s, 3H), 3.95–3.99 (m, 1H), 4.10 (dd, $J = 3.7, 12.0$ Hz, 1H), 4.34 (dd, $J = 6.6, 12$ Hz, 1H), 5.23–5.26 (m, 1H), 5.71 (dd, $J = 2.2, 2.2$ Hz, 1H), 6.04 (ddd, $J = 2.0, 3.1, 10.4$ Hz, 1H), 6.12 (dd, $J = 1.2, 2.6, 10.4$ Hz, 1H), 7.27–7.30 (m, 2H), 7.30–7.42 (m, 1H), 7.47 (m, 1H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.8, 21.1, 62.5, 64.8, 70.2, 77.2, 124.7, 126.7, 129.3, 129.6, 130.0, 131.4, 134.2, 135.9, 170.5, 170.9; $[\alpha]_{\text{D}}^{20} = 16.8$ (c 1.50, CHCl_3); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{O}_5\text{ClNa}$ $[\text{M}+\text{Na}]^+$ 347.0662, found 347.0669.

((2R,3S,6S)-3-Acetoxy-6-(4-bromophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl

acetate (3j). Following the general procedure, the crude product was purified over a silica gel column using hexane/EtOAc system (4:1) to give a colorless oil, 62 mg, 85% yield: ^1H NMR (CDCl_3 , 400 MHz) δ 2.07 (s, 3H), 2.08 (s, 3H), 3.77–3.81 (m, 1H), 4.08 (dd, $J = 3.0, 12.0$ Hz, 1H), 4.25 (dd, $J = 6.0, 12.0$ Hz, 1H), 5.27–5.29 (m, 2H), 5.97–6.00 (m, 1H), 6.12–6.16 (m, 1H), 7.26–7.29 (m, 2H), 7.48–7.51 (m, 2H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.8, 21.1, 62.8, 64.9, 69.4, 73.0, 122.4, 125.5, 129.6, 130.9, 131.7, 137.9, 170.4, 170.8; $[\alpha]_{\text{D}}^{20} = -22.0$ (c 3.00, CHCl_3); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{O}_5\text{BrNa}$ $[\text{M}+\text{Na}]^+$ 391.0157, found 391.0155.

Methyl-4-((2S,5S,6R)-5-acetoxy-6-(acetoxymethyl)-5,6-dihydro-2H-pyran-2-

yl)benzoate (3k). Following the general procedure, the crude product was purified over a silica gel column using hexane/EtOAc system (4:1 to 3:1) to give a yellow oil, 35 mg,

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6 51% yield: ^1H NMR (CDCl_3 , 400 MHz) δ 2.08 (s, 3H), 2.10 (s, 3H), 3.80–3.84 (m, 1H),
7
8 3.92 (s, 3H), 4.11 (dd, $J = 3.0, 12.0$ Hz, 1H), 4.20–4.28 (m, 1H), 5.28–5.30 (m, 1H), 5.36
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10 (s, 1H), 5.98–6.02 (m, 1H), 6.17–6.21 (m, 1H), 7.48 (d, $J = 8.2$ Hz, 2H), 8.04 (d, $J = 8.2$
11
12 Hz, 2H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.8, 21.0, 52.1, 62.7, 64.8, 69.7, 73.1, 125.4,
13
14 127.5, 129.8, 129.9, 130.8, 144.0, 166.7, 170.4, 170.7; $[\alpha]_{\text{D}}^{20} = -6.0$ (c 2.00, CHCl_3);
15
16 HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{20}\text{O}_7\text{Na}$ $[\text{M}+\text{Na}]^+$ 371.1107, found 371.1111.
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21 **((2R,3S,6S)-3-Acetoxy-6-(4-iodophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate**
22 **(3l)**. Following the general procedure, the crude product was purified over a silica gel
23
24 column using hexane/EtOAc system (4:1) to give a dark brown oil, 25 mg, 30% yield: ^1H
25
26 NMR (CDCl_3 , 400 MHz) δ 2.08 (s, 3H), 2.09 (s, 3H), 3.78–3.82 (m, 1H), 4.09 (dd, $J =$
27
28 3.1, 12.0 Hz, 1H), 4.26 (dd, $J = 6.0, 12.0$ Hz, 1H), 5.26–5.31 (m, 2H), 5.98–6.01 (m, 1H),
29
30 6.13–6.16 (m, 2H), 7.16 (d, $J = 8.2$ Hz, 2H), 7.72 (dd, $J = 1.8, 6.6$ Hz, 2H); ^{13}C NMR
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32 (CDCl_3 , 400 MHz) δ 20.9, 21.1, 62.9, 64.9, 69.5, 73.2, 94.1, 125.5, 129.8, 130.9, 137.7,
33
34 138.7, 170.5, 170.9; $[\alpha]_{\text{D}}^{20} = 1.4$ (c 1.00, CHCl_3); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{O}_5\text{INa}$
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36 $[\text{M}+\text{Na}]^+$ 439.0018, found 439.0014.
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44 **((2R,3S,6S)-3-Acetoxy-6-(3,5-bis(trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran-2-**
45 **yl)methyl acetate (3m)**. Following the general procedure, the crude product was purified
46
47 over a silica gel column using hexane/EtOAc system (6:1 to 4:1) to give a colorless oil,
48
49 54 mg, 64% yield: ^1H NMR (CDCl_3 , 400 MHz) δ 2.10 (s, 3H), 2.11 (s, 3H), 3.81–3.86 (m,
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51 1H), 4.16 (dd, $J = 2.9, 12.0$ Hz, 1H), 4.28 (dd, $J = 7.4, 12.0$ Hz, 1H), 5.25–5.28 (m, 1H),
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53 5.42 (d, $J = 1.84$ Hz, 1H), 6.08 (ddd, $J = 2.2, 2.8, 10.4$ Hz, 1H), 6.26 (ddd, $J = 1.5, 3.1,$
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55 10.4 Hz, 1H), 7.85 (s, 1H), 7.90 (s, 2H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.6, 21.0, 29.9,
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62.9, 64.7, 70.4, 72.0, 122.0, 126.3, 127.4, 129.9, 131.8, 132.1, 170.4, 170.8; $[\alpha]_{\text{D}}^{20} = 24.4$ (*c* 0.80, CHCl_3); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{16}\text{O}_5\text{F}_6\text{Na}$ $[\text{M}+\text{Na}]^+$ 449.0800, found 449.0811.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate

(3n). Following the general procedure, the crude product was purified over a silica gel column using hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 48 mg, 79% yield : ^1H NMR (CDCl_3 , 400 MHz) δ 2.06 (s, 3H), 2.09 (s, 3H), 3.79–3.83 (m, 1H), 4.08 (dd, $J = 3.1, 12.0$ Hz, 1H), 4.26 (dd, $J = 6.0, 12.0$ Hz, 1H), 5.28–5.30 (m, 2H), 5.98–6.01 (m, 1H), 6.19 (m, 1H), 7.04–7.08 (m, 2H), 7.36–7.40 (m, 2H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.8, 21.1, 62.8, 64.9, 69.3, 73.0, 115.3, 115.5, 125.2, 129.7, 129.8, 131.3, 134.6, 134.7, 161.4, 163.9, 170.5, 170.8; $[\alpha]_{\text{D}}^{20} = 15.8$ (*c* 2.50, CHCl_3); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{O}_5\text{FNa}$ $[\text{M}+\text{Na}]^+$ 331.0960, found 331.0958.

((2*R*,3*S*,6*S*)-3-Acetoxy-6-phenyl-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate and

((2*R*,3*S*,6*R*)-3-acetoxy-6-phenyl-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate (3o).

Following the general procedure, the crude product was purified over a silica gel column using hexane/EtOAc system (6:1 to 4:1) to give a yellow oil, 46 mg, 79% yield. ^1H NMR (CDCl_3 , 400 MHz) δ 2.07–2.09 (m, 9H), 2.11 (s, 3H), 3.83–3.87 (m, 1H), 3.92–3.96 (m, 1H), 4.10 (dd, $J = 3.1, 12.0$ Hz, 1H), 4.18–4.30 (m, 3H), 5.21–5.22 (m, 1H), 5.30–5.34 (m, 2H), 5.40–5.44 (m, 1H), 5.83 (dt, $J = 2.1, 10.3$ Hz, 1H), 5.91–6.18 (m, 1H), 7.31–7.42 (m, 10H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.8, 20.9, 21.1, 62.9, 63.8, 65.0, 65.5, 69.3, 73.7, 74.8, 77.2, 77.6, 124.9, 125.0, 127.2, 127.9, 128.3, 128.4, 128.5, 128.7, 131.5,

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6 132.8, 138.8, 139.8, 170.4, 170.5, 170.9, 171.0; HRMS (ESI) calcd for C₁₆H₁₈O₅Na
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8 [M+Na]⁺ 313.1052, found 313.1053.
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11 **((2R,3S,6S)-3-Acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate**
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13 **and ((2R,3S,6R)-3-acetoxy-6-(4-fluorophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl**
14
15 **acetate (3p).** Following the general procedure, the crude product was purified over a
16
17 silica gel column using hexane/EtOAc system (6:1 to 4:1) to give a colorless oil, 46 mg,
18
19 75% yield: ¹H NMR (CDCl₃, 400 MHz) δ 2.07 (s, 3.56H), 2.08 (s, 3.15H), 2.09 (s,
20
21 3.63H), 2.11 (s, 2.89H), 3.79–3.83 (m, 1.24H), 3.91–3.95 (m, 1H), 4.08 (dd, *J* = 3.1, 12.0
22
23 Hz, 1.28H), 4.19 (dd, *J* = 5.9, 12.1 Hz, 1H), 4.24–4.29 (m, 2.27H), 5.20 (s, 1H), 5.20–
24
25 5.30 (m, 2.45H), 5.39–5.42 (m, 1H), 5.82–5.90 (m, 2H), 5.98–6.02 (m, 1.24H), 6.13–6.16
26
27 (m, 1.25H), 7.02–7.08 (m, 4.47H), 7.29–7.33 (m, 2H), 7.37 – 7.38 (m, 2.45H); ¹³C NMR
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29 (CDCl₃, 400 MHz) δ 20.8, 20.9, 21.1, 62.8, 63.7, 64.9, 65.3, 69.3, 73.0, 74.9, 76.9, 77.2,
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31 115.3, 115.4, 115.5, 115.7, 125.2, 129.0, 129.1, 129.7, 129.8, 131.3, 132.5, 134.7, 134.7,
32
33 135.7, 135.7, 161.4, 161.5, 163.9, 163.9, 170.4, 170.5, 170.8, 171.0; HRMS (ESI) calcd
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35 for C₁₆H₁₇O₅FNa [M+Na]⁺ 331.0958, found 331.0956.
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43 **((2R,3S,6S)-3-Acetoxy-6-(4-bromophenyl)-3,6-dihydro-2H-pyran-2-yl)methyl**
44
45 **acetate and ((2R,3S,6R)-3-acetoxy-6-(4-bromophenyl)-3,6-dihydro-2H-pyran-2-**
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47 **yl)methyl acetate (3q).** Following the general procedure, the crude product was purified
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49 over a silica gel column using hexane/EtOAc system (4:1 to 3:1) to give a yellow oil, 61
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51 mg, 83% yield: ¹H NMR (CDCl₃, 400 MHz) δ 2.08 (s, 3H), 2.08 (s, 1.68H), 2.09 (s, 3H),
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53 2.11 (s, 1.77H), 3.78–3.82 (m, 1H), 3.91–3.94 (m, 0.64H), 4.09 (dd, *J* = 3.1, 12.0 Hz,
54
55 1H), 4.17–4.24 (m, 0.67H), 4.25–4.30 (m, 1.66H), 5.18 (s, 0.87H), 5.18 (s, 0.60H), 5.28–
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6 5.31 (m, 2H), 5.38–5.41 (m, 0.61H), 5.84–5.86 (m, 1.22H), 6.00 (dt, $J = 2.1, 10.4$ Hz,
7
8 1H), 6.13 –6.16 (m, 1H), 7.20–7.24 (m, 1.25H), 7.26–7.30 (m, 2H), 7.47–7.52 (m,
9 3.2H); ^{13}C NMR (CDCl_3 , 400 MHz) δ 20.8, 20.9, 21.1, 62.8, 63.6, 64.9, 65.3, 69.4, 73.0,
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11 74.8, 76.9, 77.2, 122.3, 122.4, 125.4, 125.5, 128.9, 129.6, 130.9, 131.7, 131.8, 132.0,
12
13 132.2, 137.9, 138.8, 170.4, 170.4, 170.8, 171.0; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{17}\text{O}_5\text{BrNa}$
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15 $[\text{M}+\text{Na}]^+$ 391.0157, found 391.0156.
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21 **((2R,3S,6S)-3-Acetoxy-6-(*m*-tolyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate and**
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23 **((2R,3S,6R)-3-acetoxy-6-(*m*-tolyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3r).**
24

25 Following the general procedure, the crude product was purified over a silica gel column
26 using hexane/EtOAc system (6:1 to 4:1) to give a pale yellow oil, 45 mg, 84% yield. ^1H
27
28 NMR (CDCl_3 , 400 MHz) δ 2.08 (s, 5.35H), 2.09 (s, 3H), 2.11 (s, 2.59H), 2.35 (s, 2.62H),
29
30 2.37 (s, 3H), 3.84–3.88 (m, 1H), 3.91–3.95 (m, 0.87H), 4.10 (dd, $J = 3.1, 12.0$ Hz, 1H),
31
32 4.20 (dd, $J = 6.0, 12.1$ Hz, 0.88H), 4.25–4.29 (m, 2H), 5.18 (s, 0.87H), 5.18–5.32 (m, 2H),
33
34 5.41–5.44 (m, 0.87H), 5.82 (dt, $J = 2.1, 10.3$ Hz, 0.87H), 5.93 (dt, $J = 1.6, 10.2$ Hz, 1H),
35
36 6.19 (m, 1H), 7.11–7.23 (m, 6.72H), 7.24–6.29 (m, 0.87H); ^{13}C NMR (CDCl_3 , 400 MHz)
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38 δ 20.8, 20.9, 21.1, 21.4, 21.5, 62.9, 63.8, 65.1, 65.5, 69.3, 73.7, 74.8, 77.2, 77.7, 124.4,
39
40 124.8, 124.9, 124.9, 128.0, 128.4, 128.6, 128.6, 129.0, 129.2, 131.6, 132.9, 138.2, 138.4,
41
42 138.8, 139.7, 170.4, 170.5, 170.9, 171.0; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5\text{Na}$ $[\text{M}+\text{Na}]^+$
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44 327.1208, found 327.1204.
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52 **Acknowledgement**
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Supporting Information

General experimental conditions; general synthesis of compound **4**; spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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