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Synthesis of a *C*-7 Pd-glycosyl-donor via the base promoted alkylative CO_2 trapping with 2-acetylfuran

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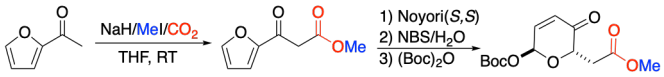

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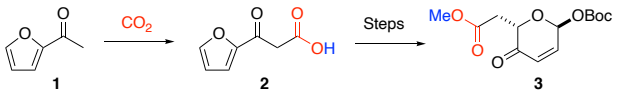
ABSTRACT

Abstract: A practical one pot alkylative carboxylation of 2-acetylfuran was developed. The reaction was optimized for the synthesis of methyl β-ketoesters. The β-keto-ester product was used in the asymmetric synthesis of a *C*-7 pyranone precursor for a Pd-glycosylation reaction, with the goal of its use in the synthesis of pyran containing natural products, such as Aspergillide C.

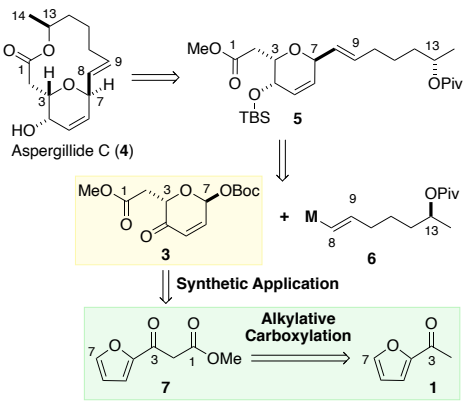
1. Introduction

An important part of future efforts to address the global impact of CO_2 on the environment is the ability to chemically modify it into a benign material,[1] which is known as carbon capture.[2] This is most effective when the newly formed product has an economic utility (*e.g.*, formic acid, methanol).[3] Thus, the production of this material will defray the cost of chemical capture, as carbon-carbon bond formation is a key transformation in chemical synthesis.[4] The carboxylation of enolizable ketones for the formation of β-ketoacids (e.g., **1** to **2**) is a potential candidate for an economically viable CO_2 capture reaction.[5] In this context, we became interested in the carboxylation of 2-acetylfuran (**1**) and the use of the product of this reaction in synthesis (Schemes 1 and 2), with the goal of expanding its synthetic and hence economic utility.[6] This synthetic approach is part of a larger effort aimed at exploring the stereochemical structure activity relationship (S-SAR) study of pyran containing polyketide natural products.[7,8,9]



Scheme 1: *Carboxylation of 2-acetylfuran **1** to form β-ketoacid **2***

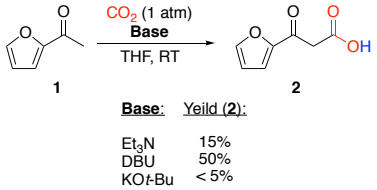
The specific synthetic application that we envisioned was one ultimately aimed at the synthesis of Aspergilide C (Scheme 2).[10,11] There have been three syntheses of Aspergillide C. The effort we envision hues most closely to the synthesis accomplished by Srihari,[12] where they prepare a protected seco-acid like **5** from a pyranone with a Pd-π-allylic forming leaving group (*e.g.*, **3**). More specifically, we were interested in the synthesis of pyranone **3**,[13] which could serve as a Pd-glycosyl donor in a *C*-glycosylation reaction with alkene **6** to form **5**, a protected precursor to seco-acid of Aspergillide C. The synthesis of **3** in turn would result from a Noyori/Achmatowicz/acylation approach from β-ketoester **7**.[14] Finally, β-ketoester **7** could be formed from 2-acetylfuran **2** by a two-step carboxylation and alkylation sequence. Herein we describe our efforts to develop a general *de novo* asymmetric synthesis of Pd-pyranone donor **3**, which revolves around the discovery of an alkylative carboxylation of 2-acetylfuran **1**.



Scheme 2: *Retrosynthesis of Aspergillide C*

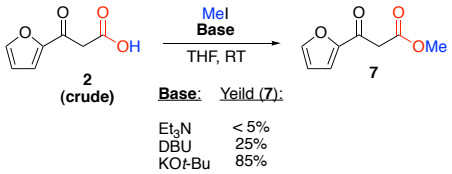
2. Results and Discussion

Previously, Jessop disclosed their study of amine catalyzed processes leading to the carboxylation of enolizable aromatic ketones.[6] More specifically, the conversion of 2-acytylfurans **1** to the β-ketoacid **2**. These studies found that amine bases like triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed the carbonylation of 2-acetylfuran **1** to form **2**. Although technically a catalyst, as the amine is recovered unchanged from the reaction, these reactions require at least one equivalent of amine because the initial product before purification is an ammonium carboxylate. Most of these procedures utilized high CO_2 pressure, in contrast, we were only interested in reaction conditions that require 1 atm of CO_2. When we explored the carboxylation reaction of 2-acetylfuran with triethylamine and DBU with 1 atm of CO_2, low to moderate yields of **2** were found (Scheme 3).



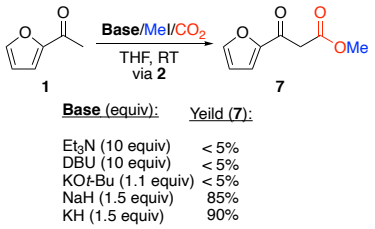
Scheme 3: *Base catalyzed carboxylation of 2-acetylfuran **1***

The choice of the amine base is important for these reactions as it requires a balance between basicity and nucleophilic reactivity toward CO_2.[15] While we were able to find conditions that provide good conversions to the β-ketocarboxylic acid **2**, we were not able to isolate the neutralized product without decarboxylation. Thus, a significant amount of 2-acetylfuran **1** was also formed upon acidification of the reaction and the chromatographic purification of **2**.[16] Of the bases we explored using DBU distinguished itself in that it provided the greatest conversion of to β-keto-carboxylic acid **2**, whereas *t*-BuOK gave little to no product. We associated the lack of reactivity of the alkoxide bases with a competing side reaction with CO_2 (*i.e.*, *t*-BuOK with CO_2 to form potassium *t*-butyl carbonate).



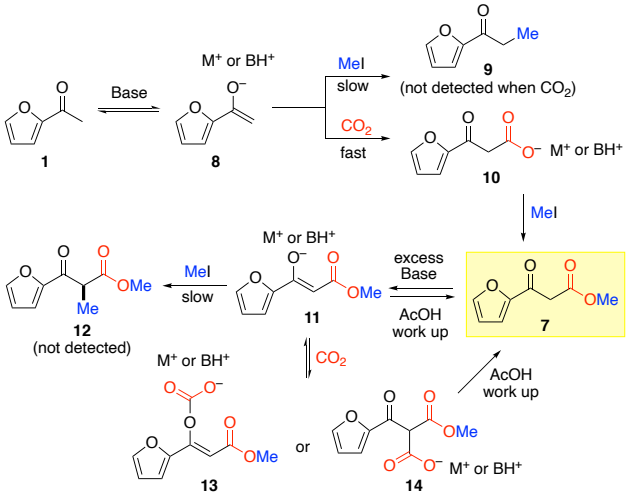
Scheme 4: *Base promoted alkylation of β-keto-carboxylic acid **2***

To confront the issue associated with decarboxylation upon isolation,[17,18] we decided to explore the possibility of capturing the *in situ* formed carboxylate anion of **2** with an S_N2 alkylation reaction.[19] The results from these efforts are outlined in Scheme 4. Only meaningful results could be garnered when using the crude product **2** prepared via the DBU promoted carboxylation of **1** (Scheme 3). When freshly isolated **2** from the carboxylation reaction was re-exposed to amine bases (*e.g.*, triethylamine and DBU) and excess MeI the desired β-ketoester **7** was detected. Interestingly, only meaningful amounts of β-ketoester **7** were formed when the stronger amine base DBU was used. In contrast to the carboxylation reaction, when the crude product from the carboxylation reaction **2** was exposed to a combination of *t*-BuOK and MeI, significant amount of the desired product **7** was isolated. This suggests that the potassium carboxylate salt of **7** was the better nucleophile in the S_N2 alkylation reactions. Unfortunately, when the MeI electrophilic component was replaced with other alkyl halides, no analogous ester products were detected (*e.g.*, EtI, BnBr).[19]



Scheme 5: *Alkylative/carboxylation of 2-acetylfuran **1** (**1** to **7**)*

These somewhat mixed results informed our efforts to develop a one-pot direct alkylative carboxylation of 2-acetylfuran **1** (Scheme 5). Not surprisingly, when we explored the use of variable amounts (1 to 10 equiv) of amine bases (*e.g.*, Et_3N and DBU) in the direct carboxylation of **1** to form **7** with MeI and one atmosphere of CO_2, it gave only trace amounts of the desired product. Similarly, the use of *t*-BuOK led to no detectable formation of **7**. In contrast to these soluble bases, successful reaction conditions were found when we explored insoluble inorganic bases, such as when NaH was used. For instance, excellent yields of **7** were formed when 2-acetylfuran **1** was exposed to a slight excess of NaH (1.5 equiv) and MeI (2 equiv) under **1** atmosphere of CO_2 in THF at 0 °C and warmed to room temperature. Even better yields of **7** were formed when NaH was replaced with the more reactive insoluble inorganic base KH. It is important to note that along with greater reactivity, KH is significantly more pyrophoric than NaH. As a result, we preferred to use NaH. More specifically, the form of NaH that is freshly liberated from parafilm by washing with dry hexanes (Scheme 5).

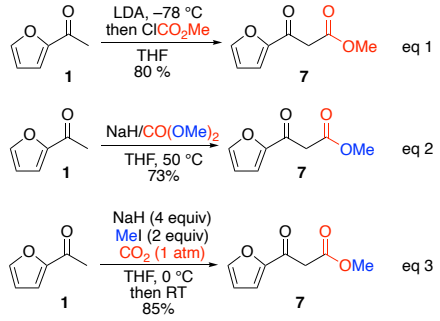


Scheme 6: *Proposed mechanism for the alkylative carboxylation*

It is important to note that when no CO_2 was present significant amounts of 2-acetylfuran alkylation products could be detected under conditions when KH, NaH, KOt-Bu and DBU were used as bases. Interestingly, no alkylation products of **7** were observed despite the fact that excess base (NaH or KH) and MeI were used under the optimized conditions. This suggest that CO_2 at ~ 1 atm is a more competent electrophile than MeI and that the resting state of the reaction might be carboxylate salt (*e.g.*, **13** or **14**), which decarboxylates upon workup. These observations led us to suggest the following mechanistic rationale for the reaction sequence (Scheme 6). The key insight to this analysis is that the reaction of enolate **8** with CO_2 must be significantly faster than with MeI. In addition, it is reasonable to assume that the product **7** is also deprotonated under these reaction conditions (*i.e.*, **7** to **11**), which

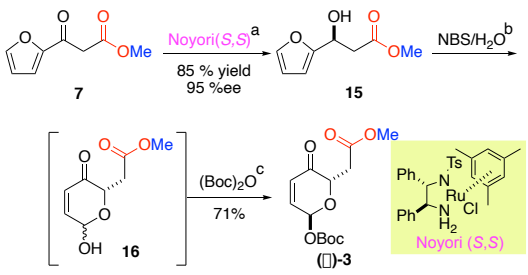
leads to the suggestion that enolate **11** reacts too slowly with MeI. Alternatively, enolate **11** may also react with CO_2 and the resulting carboxylate salt (*e.g.*, **13** or **14**) reacts too slowly with MeI. Presumably whatever products are formed they all react with acetic acid upon work up to liberate the desired product **7** upon work up of the reaction.

In the process of our development and optimization of the alkylative carboxylation reaction, we explored other methods for the conversion of **1** to **7** (Scheme 7). More specifically, the use of LDA and $ClCO_2Me$ at –78 °C gave **7** in 80% yield.[12] Similarly, **7** can be formed in an 85% yield from a mixture of 2-acetylfuran **1**, NaH and dimethyl carbonate at 50 °C. When comparing the three methods for the conversion of **1** to **7** (Scheme 7), it is important to look beyond the traditional benchmarks of number of steps and overall yield, as this simplistic analysis hides important element of synthetic efficiency and green chemistry principles. For example, the first alternative reaction in Scheme 7 (eq 1) uses highly reactive, air and moisture sensitive reagents (LDA and $ClCO_2Me$) that are difficult to prepare and requires the use of cold temperatures (–78 °C). The second reaction (eq 2) is preferable as it uses NaH and dimethyl carbonate instead of LDA and $ClCO_2Me$. However, it should be noted that dimethyl carbonate is a reagent that is made from CO_2 and thus is not preferable to CO_2 as a reagent. Thus, our preferred procedure (eq 3) can be optimized to provide multi-gram quantities of **7** from **1** in excellent yield with minimal chromatographic purification.



Scheme 7: *Alternative syntheses of 7 from 2-acetylfuran 1*

Finally, we demonstrated the utility of the alkylative carboxylation of **1** to **7** in the conversion of β-ketoester **7** into the desired pyranone **3**. The synthesis of pyranone **3** began with an asymmetric Noyori hydrogen transfer reduction (HCO_2H/Et_3N, (*S,S*)-Noyori)[20] of furan ketone in **7** into a furan alcohol **15** in excellent yield (85%) and enantiomeric excess (>95% ee). The furan alcohol **15** was oxidatively hydrated into pyranone **16** upon exposure to the Achmatowicz conditions (NBS in buffered THF/H_2O).[21] The crude pyranone **16** was diastereoselectively converted into Boc-protected pyranone **(α)-3** in 71% yield over the two steps (Scheme 8).[22]



Scheme 8: *Synthesis of pyranones (α)-3*

Reagents and conditions: (a) HCO_2H/Et_3N, (*S,S*)-Noyori ((*R*)-Ru(η^6-mesitylene)-(*S,S*)-TsDPEN), CH_2Cl_2, 85%; (b) NBS, THF, H_2O, 0 ºC; (c) Boc_2O, DMAP CH_2Cl_2, 71% (2 steps).

3. Conclusion

In conclusion a practical one pot alkylative carboxylation of 2-acetylfuran **1** to form β-ketoester **7** was developed. The synthesis of **7** was comparable in terms of synthetic efficiency to other known methods and preferable when viewed from the perspective of green chemistry. The utility of the procedure was demonstrated by its use in a gram scale stereoselective synthesis of pyranone **(α)-3**. The use of this protocol in the synthesis of complex molecules will be reported in due course.

4. Experimental section

Section A: General methods

Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon or nitrogen using oven-dried glassware and standard syringe/septa techniques. Ether, tetrahydrofuran, methylene chloride and methanol were dried by passing through activated alumina column with argon. Hexanes refer to the petroleum fraction of boiling point 40-60 °C. Commercial reagents were used without purification unless otherwise noted. Flash chromatography was performed using the indicated solvent system on silica gel standard grade 60 (230-400 mesh). R_f values are reported for analytical TLC using the specified solvents and 0.25 mm silica gel 60 F254 plates that were visualized by UV irradiation (254 nm) or by $KMnO_4$ or anisaldehyde staining. Optical rotations were obtained using a digital polarimeter at sodium D line (589 nm) and were reported in concentration of g/100 mL at 25 °C. ^1H and ^{13}C spectra were recorded on 600 MHz and 400 MHz spectrometer. Chemical shifts are reported relative to $CHCl_3$ (δ 7.26 ppm) for ^1H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. IR was recorded on FT-IR spectrometer; thin film was formed in $CHCl_3$ solution. Melting points are uncorrected.

Section B: Experimental Procedures

Methyl 3-(furan-2-yl)-3-oxopropanoate (7) method A:

To a solution of 2-acetyl furan **1** (6.54 g, 59 mmol) in 60 mL THF in a flamed dried flask under a nitrogen atmosphere was added dropwise a freshly prepared solution of LDA (60 mL/1.0 M, 1.02 equiv) at –78 °C. The solution was stirred at –78 °C for 30 min then methyl chlorocarbonate (7.5 g, 80 mmol) was added. After addition of glacial acetic acid followed by cold water, the mixture was extracted with ether acetate. The extracts were washed with cold water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give furan ketone **7** (7.91 g, 47 mmol, 80%) as colorless oil: R_f (10% EtOAc/hexane) = 0.15; IR (thin film, cm^{-1}) 3135, 2956, 1740, 1674, 1571, 1467, 1328, 1153, 1017, 883, 768; ^1H NMR (600 MHz, $CDCl_3$) δ 7.61 (dd, J = 1.8, 0.6 Hz, 1H), 7.27 (dd, J = 3.6, 0.6 Hz, 1H), 6.57 (dd, J = 3.6, 1.8 Hz, 1H), 3.86 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.8, 167.4, 152.0, 147.0, 118.3, 112.7, 52.5, 45.2. HRMS: Calculated for [$C_8H_8O_4$+Na^+]: 191.0320, Found: 191.0326.

Methyl 3-(furan-2-yl)-3-oxopropanoate (7) method B:

Sodium hydride (5.71 g, 0.24 mol, 4 equiv) was placed in a flask and washed with dry hexane three times, dimethyl carbonate (15.9 g, 177 mmol) and 60 mL THF was added to this flask. The mixture was heated to 50 °C, a solution of 2-acetyl furan **1** (6.54 g, 59 mmol) in 60 mL THF was added dropwise. The mixture was stirred for 1 h at 50 °C and then cooled to 0 °C. After addition of glacial acetic acid (10 mL) followed by cold water, the mixture was extracted with ether acetate (3 x 50 mL). The extracts were washed with cold water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography to give furan ketone **7** (7.23 g, 43 mmol, 73%) as colorless oil: R_f (10% EtOAc/hexane) = 0.15; IR (thin film, cm^{-1}) 3135, 2956, 1740, 1674, 1571, 1467, 1328, 1153, 1017, 883, 768; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.27 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.57 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.86 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.8, 167.4, 152.0, 147.0, 118.3, 112.7, 52.5, 45.2. HRMS: Calculated for [$C_8H_8O_4$+Na^+]: 191.0320, Found: 191.0326.

Methyl 3-(furan-2-yl)-3-oxopropanoate (7) method C:

Sodium hydride (5.71 g, 0.24 mol, 4 equiv) was placed in a flamed dried flask under a nitrogen atmosphere and washed with dry hexane three times. Dry THF (60 mL) was added to the flask the nitrogen atmosphere was replaced by CO_2 (1 atm), by a sequence of three evacuations and replacement with a CO_2 gas. With the solution at 0 °C, a solution of 2-acetyl furan **1** (6.54g, 59 mmol) and methyl iodide (17.0 g, 120 mmol, 2 equiv) in 60 mL THF was added dropwise then the mixture was heated at RT for 30 min. After addition of glacial acetic acid (10 mL) followed by cold water, the mixture was extracted with ether acetate (3 x 50 mL). The extracts were washed with cold water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give furan ketone **7** (8.43 g, 50 mmol, 85%) as colorless oil: R_f (10% EtOAc/hexane) = 0.15; IR (thin film, cm^{-1}) 3135, 2956, 1740, 1674, 1571, 1467, 1328, 1153, 1017, 883, 768; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.27 (dd, *J* = 3.6, 0.6 Hz, 1H), 6.57 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.86 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.8, 167.4, 152.0, 147.0, 118.3, 112.7, 52.5, 45.2. HRMS: Calculated for [$C_8H_8O_4$+Na^+]: 191.0320, Found: 191.0326.

(S)-Methyl 3-(furan-2-yl)-3-hydroxypropanoate (15)

To a flask was added furan ketone **7** (173 mg, 1.03 mmol), 2 M NaCOOH in water (10 mL), cetyl trimethylammonium bromide (37.5 mg, 0.10 mmol). The mixture was stirred at RT. for 5 min, then (*S,S*)-Noyori catalyst ((*R*)-Ru(η^6-mesitylene)-(*S*,*S*)-TsDPEN) (1.3 mg, 0.002 mmol) was added. The reaction mixture was allowed to stir for 24 h. Reaction was diluted with water and the mixture was extracted with Et_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 148 mg (0.88 mmol, 85%) of furan alcohol **15** as colorless oil: R_f (30% EtOAc/hexane) = 0.18; $[\alpha]_{25}^{D}$ = – 24 (c = 1.0, MeOH); IR (thin film, cm^{-1}) 3450, 2956, 1733, 1439, 1362, 1284, 1163, 1011, 884, 805, 741; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (dd, J = 1.8, 0.6 Hz, 1H), 6.33 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.277 (ddd, J = 3.0, 0.6, 0.6 Hz, 1H), 5.14 (ddd, *J* = 9.0, 4.2, 0.6 Hz, 1H), 3.75 (s, 3H), δ 2.91 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.83 (dd, *J* = 16.8, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 154.7, 142.2, 110.2, 106.3, 64.1, 51.9, 39.6.

(S)-Methyl 2-(6-hydroxy-3-oxo-3,6-dihydro-2H-pyran-2-yl)acetate (16)

To a solution of furan alcohol **15** (100 mg, 0.59 mmol) in 4 mL THF-H_2O (3:1) was added $NaHCO_3$ (98.8 mg, 1.18 mmol), $NaOAc•3H_2O$ (80 mg, 0.59 mmol) and NBS (105 mg, 0.59 mmol) at 0 °C. The reaction mixture was kept stirring at this temperature for 1h, then saturated $NaHCO_3$ was added to quench the reaction. The reaction mixture was extracted with EtOAc, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give 87 mg (0.47 mmol, 80%) of pyranol **16** as colorless oil: R_f (30% EtOAc/hexane) = 0.14. The mixture of diastereomers was used as is in the next step.

Methyl-2-((2S,6S)-6-(tert-butoxycarbonyloxy)-3-oxo-3,6-dihydro-2H-pyran-2-yl)acetate ((α)-3)

To a solution of crude pyranol **16** (70 mg, 0.376 mmol) in 3 mL CH_2Cl_2 was added DMAP (4.6 mg, 0.0376 mmol) at –78 °C, a pre-cooled solution of $(Boc)_2O$ (164 mg, 0.75 mmol) in 2 mL CH_2Cl_2 was added dropwise. The reaction mixture was stirred at –78 °C for 12 h. The reaction mixture was diluted with EtOAc and quenched with saturated $NaHCO_3$, extracted with EtOAc, washed (NaCl), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography to give Boc-pyranone (α)-**3** 76 mg (0.27 mmol, 71%) as light yellow oil: R_f (35% EtOAc/hexane) = 0.71; $[\alpha]_{25}^{D}$ = + 34.2 (c = 1.0, MeOH); IR (thin film, cm^{-1}) 2919, 1744, 1702, 1371, 1275, 1159, 946, 849; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (dd, J = 10.2, 3.6 Hz, 1H), 6.33 (d, *J* = 3.6 Hz, 1H), 6.25 (d, *J* = 10.2 Hz, 1H), 4.91 (dd, *J* = 6.0, 4.2 Hz, 1H), 3.68 (s, 3H), 2.95 (dd, J = 16.8, 4.8 Hz, 1H), 2.85 (dd, *J* = 16.8, 6.0 Hz, 1H), 1.52 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ193.8, 170.3, 151.7, 140.8, 128.5, 88.9, 83.7, 72.4, 51.9, 35.1, 27.6; HRMS: Calculated for [$C_{13}H_{18}O_7$+Na^+]: 309.0945, Found: 309.0946.

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6. **Author Contributions:**

§ Co-first authors, the order is alphabetical.

7. Supplementary data:

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR for all new compounds can be found in the supplementary data) associated with this article can be found, in the online version, at…

8. References and notes

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