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Multicomponent synthesis of pyroglutamic acid derivatives *via* Knoevenagel–Michael-hydrolysis-lactamization-decarboxylation (KMHL-D) sequence†

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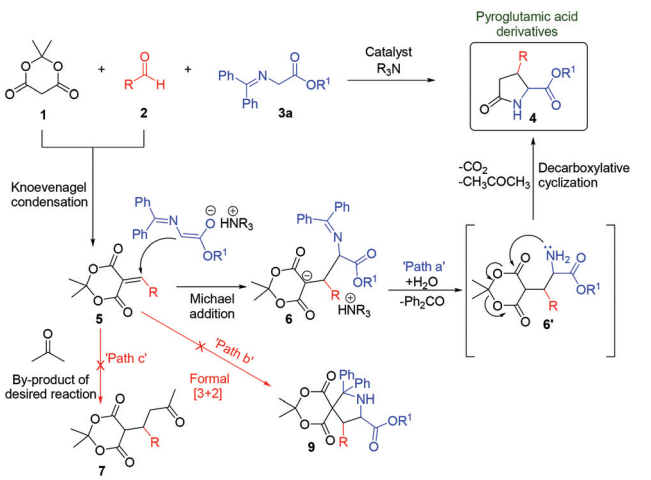
A novel and practical method for the synthesis of 3-substituted pyroglutamic acid derivatives is described. One pot multicomponent reaction of Meldrum's acid, aldehyde and Schiff's base followed an unprecedented chemoselective Knoevenagel–Michael-hydrolysis-lactamization domino sequence to afford 4-carboxy 3-substituted pyroglutamic acid derivatives under mild conditions. A carboxy intermediate formed appears to accelerate its own formation. The generality of the synthesis is exemplified by the use of a wide variety of aldehydes including enolizable aliphatic aldehydes, while substrates are stable under reaction conditions.

Introduction

Pyroglutamic acid and its derivatives are a valuable class of compounds, being found ubiquitously in various natural products and pharmaceuticals.[1] Their core structure can be transformed easily into functionalized piperidines and pyrrolidinones which find extensive applications in peptidomimetics[2] and neuroexcitatory chemistry.[3] Because of these important applications, synthesis of the pyroglutamic acid scaffold is a highly desirable target. Pyroglutamic acid and its derivatives have been synthesized by multicomponent as well as by multistep approaches, with the multicomponent strategy having proven to be a fruitful synthetic tool.[4] An Ugi reaction of keto-acid, ammonium acetate and isocyanide provides a quick access to the pyroglutamyl amide framework.[4a–e] In addition, Lavilla[4e] and Huo[4g] have reported multicomponent construction of *N*-aryl pyroglutamic acid derivatives from anilines, α-oxoaldehydes and α-angelica lactones. The principal shortcomings of these procedures are limited substrate scope and limited toleration of substituents on the lactam ring. Therefore, the development of a facile and general protocol to address these shortcomings is of considerable importance. Herein, we report a practical multicomponent synthesis of pyroglutamic esters providing a new entry to the synthesis of substituted pyroglutamic acid derivatives. Alkylidene Meldrum's acid **5**, as an excellent Michael acceptor, is utilized in various C–C and C–N bond-forming Michael addition reactions leading to a range of chiral Meldrum's acid derivatives and biologically active compounds.[5,6] It also acts as an excellent C3 synthon for several synthetic applications. Taking this into account, we planned a novel multicomponent route to access pyroglutamic esters (Scheme 1).



Scheme 1 Proposed synthesis of pyroglutamic ester *via* KMHL-D sequence.

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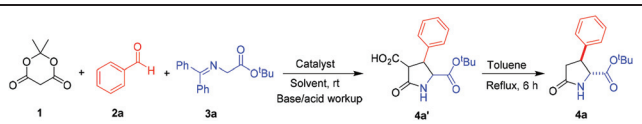
Our proposed synthetic route (Scheme 1) uses a novel chemoselective Knoevenagel–Michael-hydrolysis-lactamization-decarboxylation (KMHL-D) sequence. Kobayashi[7a] and several other groups have reported stepwise formal [3 + 2] cycloaddition reaction of a Schiff's base and an α,β-unsaturated ester for the synthesis of highly substituted pyrrolidine derivatives.[7] In this regard, the possibility of a competitive formal [3 + 2] cycloaddition reaction between Schiff's base **3a** and alkylidene Meldrum's acid **5** is an alternative outcome for the proposed reaction (Scheme 1, path b). We naively assumed that Schiff's base may undergo Michael addition with α,β-unsaturated alkylidene Meldrum's acid **5** followed by lactamization to give the corresponding pyroglutamic ester **4** (Scheme 1, path a).[8] The second challenge is to suppress the formation of compound **7** by an undesired Michael addition of acetone (a by-product of the desired reaction) to alkylidene Meldrum's acid **5** (Scheme 1, path c).[9]

To test the feasibility of the desired sequence, we carried out a model reaction of Meldrum's acid **1**, benzaldehyde **2a** and Schiff's base **3a** [*N*-(diphenylmethylene)glycine *tert*-butyl ester] in the presence of 20 mol%[10] of Lewis base[11] such as Et_3N as a catalyst in chloroform at rt (Table 1, entry 1). We observed that alkylidene Meldrum's acid **5a** underwent further reaction with Schiff's base **3a** to afford the undecarboxylated acid intermediate **4a′** in 72% yield after 24 h. It is interesting to note that the formal [3 + 2] cycloaddition product did not form even after prolonged reaction time. Attempt to decarboxylate **4a′** *in situ* by heating the reaction mixture afforded the desired product **4a** (*tert*-butyl 2-phenyl pyroglutamate) along with traces of inseparable impurities. Alternatively, upon base/acid work-up of the undecarboxylated product **4a′** followed by reflux in toluene for 6 h, the desired product **4a** was obtained in 65% yield with good diastereoselectivity (3.6 : 1, Table 1, entry 1) free of any side products. The structure of **4a** was confirmed by NMR and its relative stereochemistry was assigned by single crystal XRD analysis (see ESI, section 3†).[12] Gratifyingly, the proposed reaction took place in one pot albeit with only a trace amount of Michael addition by-product **7a** (see Scheme 1). In order to achieve the decarboxylation *in situ* and to fully suppress the formation of by-product **7a**, we screened a series of Lewis base organocatalysts such as DBU, Hünig's base, DMAP and DABCO.[11] Even though all these catalysts afforded the corresponding **4a′** smoothly, they proved ineffective for the decarboxylation of intermediate **4a′** at rt under various solvent conditions and prolonged reaction times (Table 1, entries 2–10). The desired reaction did not work in polar solvents such as DMSO, DMF and water (Table 1, entries 11–13).

These results prompted us to explore the use of phase transfer catalysis under alkaline conditions for the decarboxylation of intermediate acid **4a′**. Surprisingly, the reaction of **1**, **2a** and **3a** in the presence of nBu_4NBr (5 mol%) as a phase transfer catalyst with a stoichiometric amount of base (NaOH, 1 equiv.) in a water-rich biphasic solvent system was unsuccessful even

Table 1 Screening of catalysts and solvents[a,b,c,d]



Entry	Catalyst (mol%)	Solvent	**4a** Yield[b] (%)	*dr*[c] (*trans*/*cis*)
1	Et_3N (20 mol%)	$CHCl_3$	65	3.6 : 1
2	DBU (20 mol%)	$CHCl_3$	62	3.0 : 1
3	DMAP (20 mol%)	$CHCl_3$	59	3.5 : 1
4	DABCO (20 mol%)	$CHCl_3$	61	3.5 : 1
5	$iPrNEt_2$ (20 mol%)	$CHCl_3$	68	3.6 : 1
6	$iPrNEt_2$ (20 mol%)	ACN	52	3.7 : 1
7	$iPrNEt_2$ (20 mol%)	THF	50	3.6 : 1
8	$iPrNEt_2$ (20 mol%)	MTBE	51	3.1 : 1
9	$iPrNEt_2$ (20 mol%)	Toluene	66	3.3 : 1
10	$iPrNEt_2$ (20 mol%)	EtOAc	62	3.6 : 1
11	$iPrNEt_2$ (20 mol%)	DMSO	NR	—
12	$iPrNEt_2$ (20 mol%)	DMF	NR	—
13	$iPrNEt_2$ (20 mol%)	Water	NR	—
14[d]	nBu_4NBr (5 mol%)	H_2O : toluene(5 : 1)[d]	NR	—
15	nBu_4NBr (5 mol%)	H_2O : toluene(5 : 1)	55	3.6 : 1
16	—	H_2O : toluene(5 : 1)	61	3.6 : 1
17	—	Toluene	58	3.6 : 1
18	—	$CHCl_3$	53	3.6 : 1
19	—	**EtOAc**	**65**	**3.6 : 1**
20	—	MeCN	56	3.5 : 1
21	—	MTBE	54	3.5 : 1

[a] Reaction conditions: Meldrum's acid **1** (1.4 mmol, 1 equiv.), benzaldehyde **2a** (1.47 mmol, 1.05 equiv.), Schiff's base **3a** (2.1 mmol, 1.5 equiv.) catalyst (5–20 mol%), various solvents at rt for 24 h, then base/acid workup followed by reflux in toluene for 6 h for decarboxylation. [b] Isolated yield after purification by column chromatography. [c] *dr* was calculated by ^1H NMR. [d] 1 equiv. of NaOH used. NR-No reaction.

after prolonged reaction time (Table 1, entry 14). We conclude that the desired Knoevenagel condensation did not proceed to afford **5a** because of the requirement for the acid catalysis from Meldrum's acid **1** (pK_a 4.9),[6b] voided by the addition of NaOH. However, it is interesting to note that acid intermediate **4a′** was isolated in 66% yield when a neutral phase transfer condition was employed without addition of a strong base.[13] Subsequently, isolated acid **4a′** was refluxed in toluene to obtain the desired product **4a** in 55% yield with good diastereoselectivity (Table 1, entry 15). These results suggest that the desired reaction may proceed under neutral conditions without additional catalysis to furnish intermediate **4a′**. This conclusion was further supported by the fact that reaction proceeded smoothly in the absence of any external catalyst or base to afford the intermediate **4a′** and eventually affording desired product **4a** with good yield (Table 1, entry 16).

These results led us to believe that the reaction is catalyzed by the trace amount of primary amine catalyst **3a′** which may be present along with the starting material **3a** or due to primary amine catalyst **3a′** generating *in situ via* hydrolysis of Schiff's base **3a** (Scheme 2). We surmise that relatively acidic Meldrum's acid **1** may catalyze the hydrolysis of Schiff's base **3a** to afford the primary amine **3a′**.

In order to optimize the reaction conditions, we screened the reaction in different solvents (Table 1, entries 17–21) and ethyl acetate proved to be the optimum solvent for the reaction (using base/acid workup followed by refluxing in toluene for 6 h) to afford desired product **4a**. While *in situ* formation of **4a′** was confirmed by ^{1}H NMR (see ESI, section 1†), the base/acid work up proved to be necessary for obtaining the intermediate **4a′** in good yield.

In order to investigate and validate the role of Meldrum's acid **1** for the hydrolysis of Schiff's base **3a**, we carried out a reaction of Schiff's base **3a**, Meldrum's acid **1** (1 equiv., pK_a 4.9 in water) and a stoichiometric amount of water in ethyl acetate. The reaction was monitored by time dependent proton NMR spectroscopy. The formation of benzophenone over a period of time clearly indicates that the hydrolysis of Schiff's base **3a** in the reaction mixture (Scheme 2, see ESI, section 1† for NMR study). On the other hand, we did not observe the hydrolysis of Schiff's base **3a** when stirred with water for a prolonged reaction time in the absence of Meldrum's acid **1**. This result established the catalytic role of Meldrum's acid **1** in the reaction pathway or its necessity in the hydrolysis of Schiff's base **3a**.

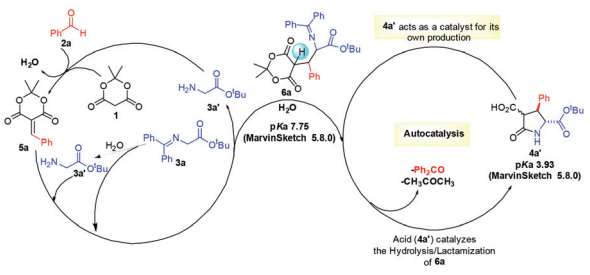
To understand the role of *in situ* generated water during the reaction, we performed the reaction in the presence of molecular sieves (4 Å). We observed that Meldrum's acid **1** was completely consumed to afford the intermediate **6a** (confirmed by HRMS, see ESI, section 1†) in 6 h. We believe that a trace amount of primary amine **3a′** present along with starting material **3a** may have catalyzed the reaction to form intermediate **6a** in the absence of water. Attempts to isolate **6a** using chromatography (silica gel) only resulted in compound **4a′**.

Based on the experimental evidence, we propose that slow hydrolysis of Schiff's base **3a** generates primary amine catalyst *tert*-butyl glycinate **3a′** that catalyzes the Knoevenagel condensation of Meldrum's acid **1** and benzaldehyde **2a** to generate Knoevenagel product **5a**. The Michael addition of Schiff's base **3a** to **5a** affords intermediate **6a**. Further, the acidic nature of the reaction medium initiates hydrolysis followed by lactamization of intermediate **6a** to afford undecarboxylated pyroglutamate ester **4a′** (Scheme 2). We surmise that further acid catalyzed conversion of intermediate **6a** into carboxylic acid **4a′** is probably autocatalytic[14] involving acid **4a′** catalyzed hydrolysis of imine **6a** [**4a′** (pK_a 3.93) is stronger acid than intermediate **6a** (pK_a 7.75) and Meldrum's acid **1** (pK_a 4.9)].

In order to understand further, we proposed to conduct kinetic analysis by monitoring on the yield of **4a′** during the reaction by time dependent ^{1}H-NMR.[15] This analysis showed that Meldrum's acid **1** and benzaldehyde **2a** were almost completely consumed within 15 min (see Appendix I, ESI, section 1†). We further observed that the formation of **4a′** proceeded slowly at first leading to a rapid and significant increase in the yield of **4a′**, whose, yield remained almost constant after 6 h (see Appendix I, ESI, section 1†). We believe that the initial slow hydrolysis of **6a** is due to the low concentration of **4a′** (induction period, up to 1 h, see Fig. 1). However, the rate of hydrolysis of **6a** and the subsequent formation of **4a′** increases rapidly with the increase in concentration of **4a′**.

The rate of formation of product **4a′** increased rapidly (after 1 h) and then levelled off, complimentary to the rise and fall in the yield of intermediate **6a** (Fig. 1, red and black curves). These data show the yield of **4a′** follows a sigmoidal curve after an induction period of 1 h, probably signature of the autocatalytic process. The addition of **4a′** (10 mol%) to the reaction did not discernibly reduce the initial lag period,[14b] though this might have been a consequence of experimental time limitation. It seems likely that the required acidic environment must be present from the outset to initiate hydrolysis of intermediate **6a** and this may be provided by Meldrum's acid **1** and later during the course of the reaction by **4a′**. The result of kinetic analysis is in accordance with the experimental results on yields.

Having optimized reaction conditions in hand, the scope of the KMHL-D three component reaction was investigated by the use of a range of aldehydes (**2a–2t**) and two Schiff's bases (**3a**, **3b**) (Table 2).



Scheme 2 Plausible reaction mechanism.

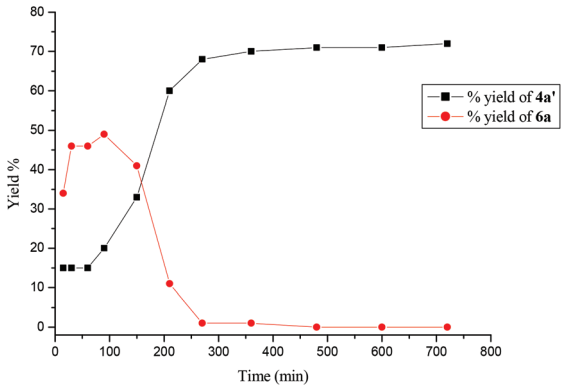
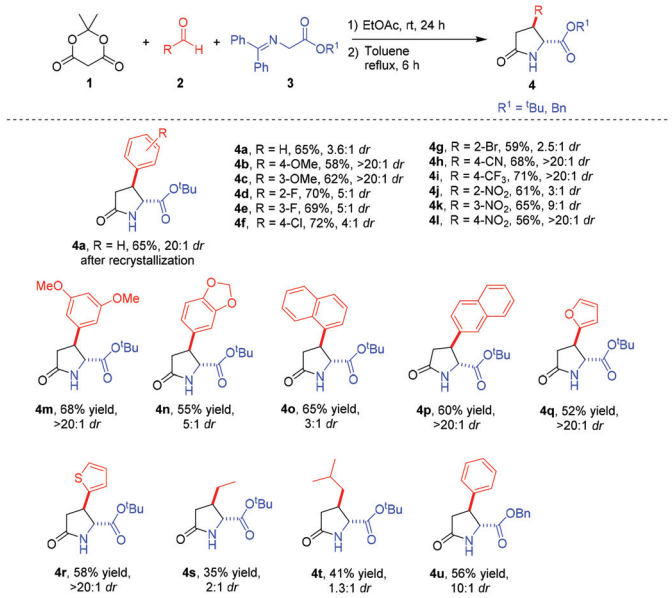


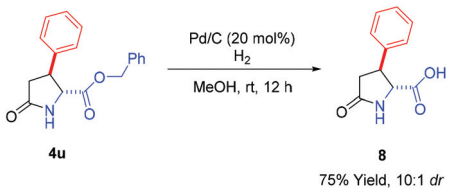
Fig. 1 ^{1}H NMR analysis of the formation of **4a'**. ^{1}H-NMR kinetic experiments for the reaction of Meldrum's acid **1** (300 mg, 2.08 mmol), benzaldehyde **2a** (225 μL, 2.2 mmol), Schiff's base **3a** (800 mg, 2.7 mmol) and 1,3,5-trimethoxy benzene (350.1 mg, 2.08 mmol, as an internal standard) in 8 mL ethyl acetate at room temperature (25 °C). To quantify the time course of this reaction, we followed the production of **4a'** by ^{1}H NMR spectroscopy. Aliquots were sampled at various time intervals, solvent (EtOAc) evaporated, and the residue dissolved in $CDCl_3$ for NMR analysis.

Table 2 Substrate scope[a,b,c]



[a] Reaction conditions: Meldrum's acid **1** (1.4 mmol, 1 equiv.), aldehyde **2** (1.47 mmol, 1.05 equiv.), Schiff's base **3** (2.1 mmol, 1.5 equiv.) in EtOAc at rt, 24 h then then base/acid workup followed by reflux in toluene for 6 h for decarboxylation. [b] Isolated yield after purification by column chromatography. [c] *dr* calculated by ^{1}H NMR.

Different aromatic aldehydes containing electron-donating and -withdrawing functional groups led to the corresponding desired pyroglutamic esters (**4b–4n**) in moderate to good yields (up to 72% yield) with moderate to excellent diastereoselectivity (up to >20 : 1 *dr*). Similarly, bicyclic aromatic aldehydes such as 1/2-naphthaldehyde (**2o** and **2p**) and heteroaromatic aldehydes such as 2-furfural (**2q**) and 2-thiophenecarboxaldehyde (**2r**) reacted smoothly to afford **4o–4r** in good yields (up to 65%) with diastereoselectivity up to >20 : 1. In order to explore a wider scope for this method, the reaction was performed with aliphatic aldehydes. This was successful, even for enolizable aldehydes such as propanal and isovaleraldehyde leading to the corresponding pyroglutamic esters (**4s–4t**) albeit in more modest yields (up to 41%) and with limited diastereoselectivity (up to 2 : 1 *dr*). Use of the benzyl ester of Schiff's base **3b** also proved to be viable, providing product **4u** with moderate yield (56%) with good diastereoselectivity (10 : 1). The practicality of the method was demonstrated by gram scale syntheses of compounds **4a** (55% yield) and **4h** (59% yield). The *trans* stereochemistry of the major isomers of the compounds **4b–4u** was assigned based by analogy to that of compound **4a**.



Scheme 3 Deprotection of ester.

In order to demonstrate the practical utility of the protocol, pyroglutamic acid derivative **8** was prepared starting from pyroglutamic benzyl ester **4u** under hydrogenolytic conditions (Scheme 3).[16]

Conclusions

We have developed a simple, practical and mild protocol to access 3-substituted pyroglutamic acid derivatives using an unprecedented Knoevenagel–Michael-hydrolysis-lactamization-decarboxylation (KMHL-D) sequence. The reaction works well in the absence of external catalyst or facilitating reagent. This novel one pot protocol tolerates a wide variety of aldehydes including enolizable aliphatic aldehydes under mild reaction conditions. The enantioselective development of this reaction is in progress.

Experimental section

General methods

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purification. Meldrum's acid was purchased from Spectrochem. Aldehydes and ketones were purchased from Aldrich, Spectrochem and Alfa-aeser. Compounds **3a** and **3b** were prepared according to reported procedure.[17] All reactions were carried out in oven dried glassware. Thin-layer chromatography (TLC) was per-

formed using silica gel 60 GF254 pre-coated aluminum backed plates (2.5 mm). Visualization was accomplished by examination under UV light at 254 nm and/or ninhydrin stain. Column chromatography was performed using silica gel (200–300 mesh) eluting with petroleum ether and ethyl acetate. NMR spectra were recorded with tetramethylsilane as internal standard. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker and Jeol). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) and CD_3OD (δ = 4.87 and 3.31 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) and CD_3OD (δ = 49.00) for ^{13}C NMR spectroscopy. Coupling constants (J) are given in Hz. IR spectra were obtained using a FT-IR spectrophotometer as neat and are reported in cm^{-1}. Samples were analyzed by high-resolution mass spectrometry using ESI TOF.

General procedure for the synthesis of 3-substituted pyroglutamic acid derivative 4

In an oven-dried 10 mL round bottom flask with a Teflon-coated stir bar, Meldrum's acid **1** (200 mg, 1.39 mmol, 1 equiv.) was dissolved in 6 mL of EtOAc. Then benzaldehyde **2a** (150 μL, 1.47 mmol, 1.06 equiv.) and Schiff's base **3a** (532.9 mg, 1.8 mmol, 1.3 equiv.) were added and the reaction mixture was stirred for 24 h at rt. On completion of the reaction (monitored by TLC), the reaction mixture was directly transferred in to a separating funnel and portioned between saturated aq. $NaHCO_3$ solution (25 mL) and EtOAc (20 mL). The aqueous layer containing pyroglutamic acid derivative **4a′** was separated and the bicarbonate extraction repeated twice. The combined aqueous layers were acidified with 1 N aq. HCl solution till solution became turbid (pH ~2). After which, the pyroglutamic acid derivative **4a′** was then back-extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The organic extract was evaporated under vacuum to afford **4a′**. The crude pyroglutamic acid derivative **4a′** was dissolved in 2 mL toluene and refluxed for 6 h in order to effect complete decarboxylation (monitored by TLC). Toluene was then evaporated and the crude product **4a** purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent. Product **4a** was obtained as a white solid in 65% yield.

***trans-tert*-Butyl 5-oxo-3-phenylpyrrolidine-2-carboxylate (4a).** Compound **4a** was synthesized following the general procedure and was obtained as white solid (235 mg, 65% *trans*/*cis*; 3.6 : 1, after recrystallization from DCM/*n*-hexane solvent system *trans*/*cis* 20 : 1).

M.p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.30–7.26 (m, 3H), 6.31 (s, 1H), 4.15 (d, J = 6.0 Hz, 1H), 3.68–3.63 (m, 1H), 2.85 (dd, J = 17.3, 9.5 Hz, 1H), 2.54 (dd, J = 17.3, 7.4 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 170.3, 141.9, 129.1, 127.6, 127.2, 82.8, 63.6, 44.4, 38.4, 28.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$ 262.1443, found 262.1450. FTIR cm^{-1} (neat) 3233, 2978, 2927, 1702, 1453, 1370, 1236, 1154, 845.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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