The bio-based methyl coumalate involved Morita–Baylis–Hillman reaction

Liang Chang, Serge Thorimbert, Luc Dechoux

Bio-based methyl coumalate involved Morita-Baylis-Hillman reaction

Liang Chang, Serge Thorimbert* and Luc Dechoux*

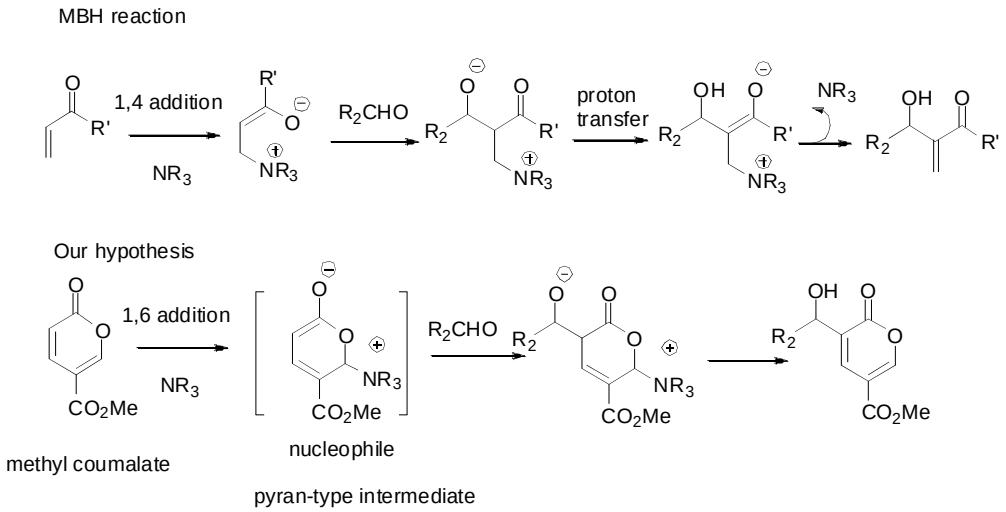
We report the first use of renewable, bio-based, non-hazardous feedstock methyl coumalate (MC) in organocatalyzed Morita-Baylis-Hillman (MBH) reactions. This atom-economical pathway employs inexpensive Et_3N as a catalyst in ethanol. Synthon MC efficiently constructs C-C bonds with various imines and aldehydes in moderate to good yields. This catalytic process is triggered via an unprecedented 1,6-conjugated addition, as opposed to the classical MBH reaction. Moreover, this methodology expands Morita-Baylis–Hillman donor capabilities to a 2-pyrone derivative for the first time. MBH adducts described herein could be applied to the synthesis of fine chemicals with biologically active structural cores, such as diphenylmethanol, hydroisobenzofurans, and hydroisoindoles.

Introduction

Transition from petroleum-based feedstocks to renewable alternatives for synthesis is a guiding principle of green chemistry.[1–8] Efficient and sustainable synthesis of fine chemicals and pharmaceuticals has both societal and commercial interest. Finding new conversion methodologies from bio-based and renewable resource are attractive research areas in academia and industry. [9,10]

Many metal-catalysed processes have been reported;[11–14] however, organocatalysis enjoys increasing favour due to its environmentally benign nature, which employs less hazardous small organic compounds as catalysts for versatile transformations.[15–17] The Morita-Baylis-Hillman (MBH) reaction represents a milestone for C-C bond formation within organocatalysis. It is atom economical and has enormous synthetic utility across a wide range of applications.[18–20] This metal-free process couples an activated alkene (Morita-Baylis-Hillman donor, MBHD) and an sp^2 electrophilic carbon (Morita-Baylis-Hillman acceptor, MBHA), in the presence of tertiary amine or phosphine. This generates densely functionalized MBH adducts in a single step, without producing any by-products or waste.[21,22] Intense academic study and industrial application of this reaction have produced large quantities of published researches and patents.[23] Unfortunately, reactants are dominated by petroleum-based chemicals, save reports of furfural and hydroxymethylfurfural as MBHA.[24,25]

Figure 1 Morita-Baylis-Hillman (MBH) reaction mechanism

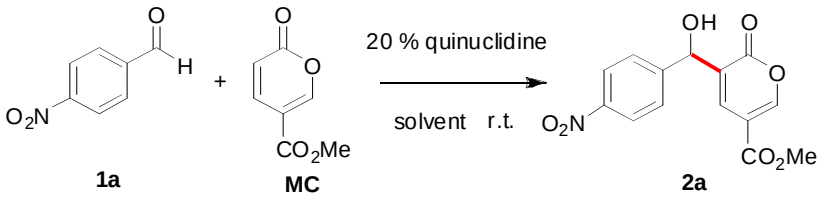


Progresses have been made towards bio-derived MBHD. Paine *et al*. and Corma *et al.* have described two bio-based pathways to acquire the acrolein and methyl vinyl ketone.[26] Recently, Beckham *et al.* reported a sustainable synthesis of acrylonitrile from ethyl 3-hydroxypropanoate.[27] Acrolein, acrylonitrile, and methyl vinyl ketone are known hazardous chemicals. They are highly flammable, very toxic, corrosive and dangerous for the environment.[28] In contrast, methyl coumalate (MC) is a non-hazardous, bio-based chemical. Produced from the dimerization of malic acid, it is a biorenewable synthon with diverse synthetic applications.[29–36] We recently discovered that MC can serve as 1,6-Michael acceptor, in the presence of certain nucleophiles.[37–39] Inspired by these findings, we began studying the nucleophilicity of the zwitterionic intermediates in the MBH catalytic pathway (Figure 1). We encoutered challenges in trapping pyran intermediates with electrophiles without side reaction competition (i.e. ring opening and decarboxylation).[40-41] Moreover, dienolates generated from 1,6-addition are, theoretically, weaker nucleophiles than regular enolates. The delocalization of negative charge on an extra π bond confers greater thermodynamic stability. In addition, the C-C functionalization of 2-pyrones remains a challenge.[42–44] To the best of our knowledge, neither the use of methyl coumalate (or other 2-pyrone derivatives) as Morita-Baylis-Hillman donors, nor the 1,6-conjugate addition-triggered MBH reaction were reported in previous literature.[45]

This research embodies four key principles of green chemistry: *less hazardous chemical syntheses, atom economy, catalysis,* and *use of renewable feedstocks*. Herein we report a novel MBH reaction, which employs bio-based feedstock, via a 1,6-conjugate addition triggered MBH mechanism.

Results and discussion

We began our investigation by optimizing the solvent. We combined *p*-nitrobenzaldehyde **1a** and methyl coumalate (**MC**) in the presence of 20 mol% quinuclidine for the room-temperature model reaction (Table 1). No reaction occurred in toluene or DMSO (entries 1, 2). Low yields were obtained in DCM and THF after 2 to 4 days (entries 3, 4). Only trace amounts of **2a** were detected with acetonitrile (entry 5). We were pleased to find that the reactions ran smoothly in protic solvents: Yields of **2a** were substantial in ethanol (24h, 62%, entry 6) and isopropanol (36h, 51%, entry 7). Furthermore, the combination of water with THF (1:1) offered no improvement on the product yield (entry 8). Based on these data, ethanol was chosen as the ideal solvent.



1a **MC** **2a**

Table 1 Optimization of the solvents[a]

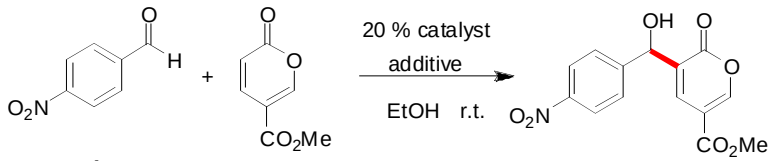
Entry	Solvent	Time (h)	Conversion	Yield %[b]
1	toluene	24	0	0
2	DMSO	48	0	0
3	THF	48	77	30
4	DCM	96	59	25
5	CH_3CN	48	100	trace
6	EtOH	24	100	62
7	*i*Pr-OH	38	100	51
8	THF/H_2O[c]	48	100	21

[a] Reaction conditions: All reactions were performed with MC (1 mmol) and *p*-nitrobenzaldehyde **1a** (1 mmol). [b] isolated yields. [C] THF : H_2O (1 : 1) mixture.

The subsequent survey of different Lewis bases in ethanol is summarized in Table 2. Notably, no reaction occurred in the absence of catalyst (entry 1). 20 mol% Ph_3P (entry 2) failed to initiate the reaction; however, the less hindered and more nucleophilic $n Bu_3P$ generated **2a** in 14% yield (entry 3). There was not a dramatic difference in catalysis between quinuclidine (entry 4), DABCO (entry 5) and Et_3N (entry 6). The salt effect was investigated to improve MBH reaction efficiency. Intriguingly, we observed a dramatic acceleration of reaction rate. Addition of 1 equiv KCl to the quinuclidine catalyst facilitates reaction completion in 4 h, affording compound **2a** in 62% yield (entry 7). Similar results (4 h, 64%, entry 8) were obtained when employing 1 equiv LiCl. To our

delight, K_2CO_3 spurred the reaction to completion in only 1.5 h (entries 9-11), whereas substoichiometric quantities were not as efficient (0.5 equiv., 6 h, 60%). These results show an optimal combination of Lewis base and salt: 20 mol% Et_3N and 1 equiv. K_2CO_3 in ethanol. In addition, synthesis could be readily scaled up to gram quantities without any difficulties, providing 2.14 g (70%) of compound **2a**. It is noteworthy that with this activated substrate **1a**, the reaction gave the expected MBH product **2a** in moderate yield, even in the absence of Lewis base (entry 12).[46]

Table 2 Optimization of the catalysts and additives [a]



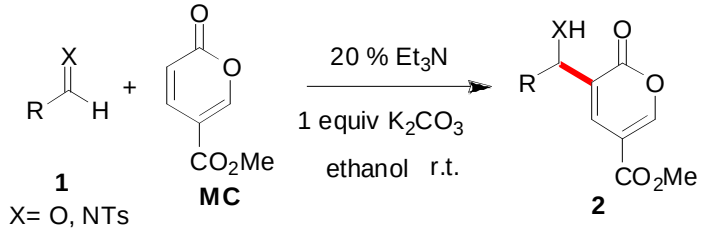
1a **MC** **2a**

Entry	Catalyst	additive [b]	Time(h)	Yield % [c]
1	/	/	24	NR
2	Ph_3P	/	24	NR
3	*n*-Bu_3P	/	96	14
4	quinuclidine	/	48	62
5	DABCO	/	48	66
6	NEt_3	/	48	56
7	quinuclidine	KCl	4	62
8	quinuclidine	LiCl	4	64
9	quinuclidine	K_2CO_3	1,5	66
10	DABCO	K_2CO_3	1,5	63
11	NEt_3	K_2CO_3	1,5	74
12	/	K_2CO_3	4	59

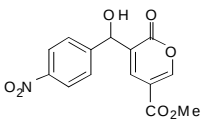
[a] Reaction conditions: All reactions were performed with MC (1 mmol) and p-nitrobenzaldehyde **1a** (1 mmol) in EtOH 3 mL. [b] 1 equiv of additive added. [c] isolated yields.

With optimized conditions in hand, we explored the scope and limitations of these reactions (Table 3). A broad range of aldehydes was tolerated. Moderate yield was achieved with benzaldehyde as MBHA (**2b**, 62%). Halogen-substituted benzaldehydes were well tolerated, delivering the expected products in yields ranging from 35 to 60% (**2c-e**). Higher yields are obtained when employing electron withdrawing groups on the aromatic ring, such as *p*-CN (**2f**, 71%), *o*-NO_2 (**2g**, 63%) and *p*-CF_3 (**2h**, 71%). The electron-rich *p*-MeO group gave lower yields (28% of adduct **2i**), since the aldehyde is less electrophilic. This catalytic system is applicable to aliphatic aldehydes. Ethanal and propanal gave the corresponding products **2j** and **2k** in 40% and 38% yields respectively. Biorenewable BHA furfural was tested, giving **2l** in 61% yield. Particularly high yields were observed with aryl N-tosyl imines as Baylis Hillman acceptors. The simplest phenyl tosyl imine produced the corresponding MBH adduct **2m** in 75% abundance. Good to excellent yields were obtained when electron deficient imines were used, affording **2n**-**2q** in yields up to 90%. For comparison, electron enriched imines provided the corresponding amine in moderate to good yield (**2r**, 86%), (**2s**, 60%). Starting from halogen substituted imines, the MBH adducts **2t**, **2u** were successfully isolated in 80% and 75% yields.

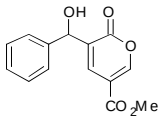
Table 3. Synthesis of bio-based MBH and aza-MBH adducts **2**[a]



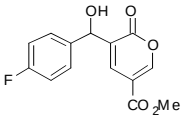
[a] isolated yields. [b] reactions were performed with 50% NEt_3 without additives.



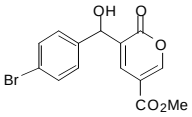
2a, 1.5 h, 74%



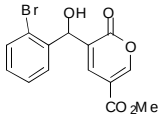
2b, 3 h, 62%



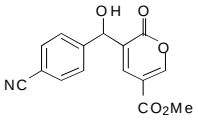
2c, 3.5 h 60%



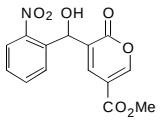
2d, 3.5 h, 55%



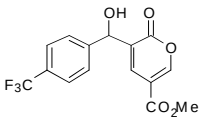
2e 2.5 h, 35%



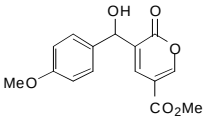
2f, 2 h, 71%



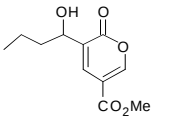
2g, 1.5 h, 63%



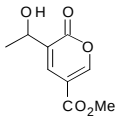
2h, 2 h, 71%



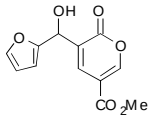
2i 3 h, 28%



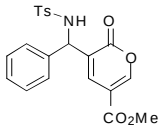
2j 3.5 h 40%



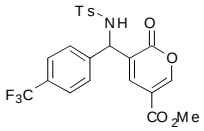
2k, 2 h, 38%



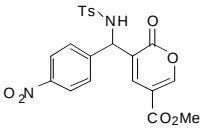
2l 2 h, 61%[b]



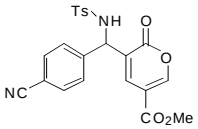
2m, 4 h, 75%



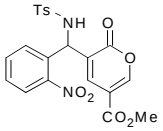
2n, 4 h, 84%



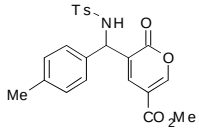
2o, 4 h, 85%



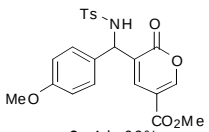
2p, 4 h, 90%



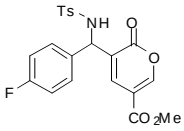
2q, 4 h, 65%



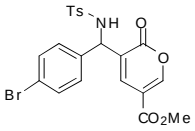
2r, 4 h, 86%



2s 4 h, 60%



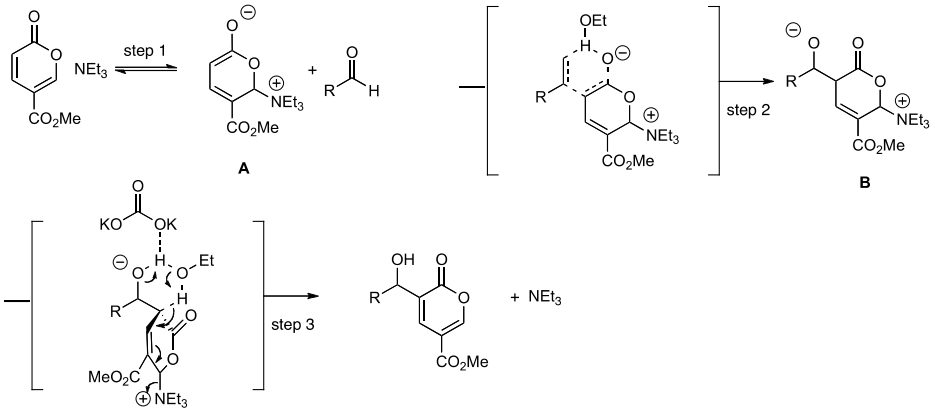
2t, 4 h, 80%



2u, 4 h, 75%

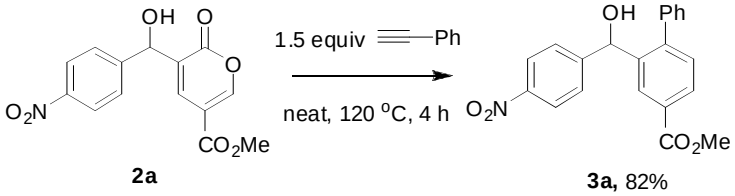
Based on experimental reports and previous publications, a tentative reaction mechanism is proposed in Scheme 1. The catalytic cycle would be initiated by conjugated 1,6 addition of trimethylamine to the electron-deficient MC, which generates the zwitterionic dienolate **A**. We presume that hydrogen bonding to the aldehyde would promote step 2[47] and ionic salts could stabilize the zwitterions **A**. The electrophiles are trapped by zwitterion **A**, leading to the formation of intermediate **B**. At this stage, the mechanistical pathway is achieved through a six-membered proton transfer from EtOH to the alkoxy with concomitant elimination of the α-proton. We postulate that this step is catalyzed by the basic potassium carbonate, accelerating step 3, which is, in the first times of the reaction, the Rate Limiting Step (RLS) as already mentioned for classical MBH reactions.[48]

Scheme 1 Plausible mechanism for the novel MBH reaction



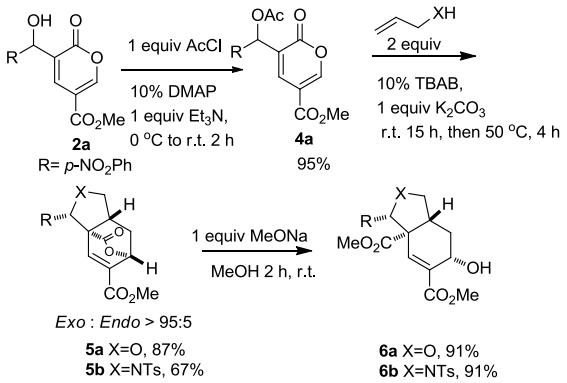
The obtained MBH adduct **2a** could be applied for the synthesis of fine chemicals, like diphenylmethanol derivatives. These are a key set of intermediates for antihistamines, antihypertensive agents, and agrochemical synthesis.[49] The reaction was carried out in solvent-free conditions, and diphenylmethanol derivative **3a** obtained in 82% yield (Scheme 2).

Scheme 2 Synthesis of diphenylmethanol derivative from MBH adduct



To further demonstrate the synthetic potential of the obtained MBH adducts, we also developed an efficient access towards hexahydro-isobenzofuran and hexahydro-1*H*-isoindole (Scheme 3). MBH adduct **2a** was first acetylated to produce **4a** in excellent yield. A one pot domino reaction, triggered by a regioselective substitution of the acetate function of **4a** with allylic alcohol or allylic tosyl amine, and followed by an intramolecular Diels-Alder reaction provided **5a** and **5b** with excellent stereoselectivity (*Exo:Endo* > 95:5) in 87% and 67% yields respectively.

Scheme 3 Transformation to hydroisobenzofuran and hydroisoindole cores



A facile alcoholysis could transform **5a**, **5b** into the highly functionalized stereopure compounds **6a** and **6b. 6a** contains the hydro-isobenzofuran core, which can be found in many bioactive natural products.[50-53] Similarly, **6b** contains the hydro-1*H*-isoindole core, which interacts with biological targets involved in many diseases: cancer, Alzheimers, antiemetics, and benign prostatic hyperplasia.[54-58]

Conclusions

We have developed a novel reaction, for efficient C-C bond formation between the non-hazardous bio-based methyl coumalate and a variety of imines and aldehydes. Et_3N serves as catalyst in ethanol for this environmentally benign transformation, which occurs via an unprecedented 1,6-conjugated addition-triggered Morita-Baylis-Hillman pathway. Remarkable rate enhancement was achieved using K_2CO_3. This atom-economical approach has broad substrate scope, readily available starting materials, inexpensive catalysts, and accessible additives. Furthermore, the MBH adducts can be applied to the synthesis of broad-spectrum pharmaceutical intermediates with biologically active structural cores, such as diphenylmethanol, hydroisobenzofuran and hydro-isoindole derivatives.

Conflicts of interest

The authors declare no competing financial interest.

Experimental section

Materials and general methods

All reactions were carried out under argon atmosphere with magnetic stirring. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C nuclei. Chemical shifts are reported in δ units, parts per million (ppm) using, for ^{1}H and ^{13}C, solvent residual peak as internal standard references: chloroform (7.26 ppm for ^{1}H NMR and 77.16 ppm). Coupling constants (*J*) are given in Hz, multiplicities are abbreviated as: s (singlet), br (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), m (multiplet). High-resolution mass spectra (HR-MS) were recorded on a LTQ-Orbitrap Mass Spectrometer [Thermo Scientific]. IR: Shimadzu IRAffinity-1CE spectrometer, wavenumbers in cm^{-1}.

Typical experimental procedure for the synthesis of compound 2 (a-u).

In a round-bottom flask corresponding aldehyde or imine **1** (1 mmol) and methyl coumalate (154 mg, 1 equiv) were mixed in 5 mL of ethanol, then Et_3N (28 µL, 0.2 equiv) and K_2CO_3 (138 mg, 1 equiv) were added. The flask was purged with Ar and then stirred at room temperature until MC was consumed and the reaction quenched with 1M HCl 5 mL. The mixture was extracted with CH_2Cl_2 (20 mL), and the layers were separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The crude product was purified by flash chromatography gave the corresponding desired product **2a**-**2u**.

Methyl 3-(hydroxyl (4-nitrophenyl) methyl) -2-oxo-2H-pyran-5-carboxylate (2a): colorless oil (226 mg, 74%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 – 8.20 (m, 1H), 8.22 – 8.07 (m, 2H), 7.90 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.68 – 7.55 (m, 2H), 5.84 (s, 1H), 3.87 (s, 3H), 3.40 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.2, 160.0, 156.8, 147.8, 147.2, 137.0, 129.2, 127.5(2C), 123.9(2C), 112.4, 70.7, 52.7; **IR** (film, cm^{-1}): 3491, 2954, 1714, 1519, 1230, 989; **HRMS** (ESI) m/z calcd for $[M+Na^+]$ $C_{14}H_{11}NNaO_5$ 328.0428, found 328.0432.

Methyl 3-(hydroxy(phenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (2b): colorless oil (155 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.5 Hz, 1H), 7.85 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.46 – 7.28 (m, 5H), 5.75 (d, *J* = 4.0 Hz, 1H), 3.87 (s, 3H), 3.01 (d, *J* = 4.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.5, 160.2, 156.3, 140.1, 136.3, 130.2, 128.7(2C), 128.4(2C), 126.7, 112.3, 71.6, 52.5; **IR** (film, cm^{-1}): 3401, 2974, 1714, 1228, 950; **HRMS** (ESI) m/z calcd for $[M+Na^+]$ $C_{14}H_{12}NaO_5$ 283.0577, found 283.0580.

Methyl 3-((4-fluorophenyl)(hydroxy) methyl)-2-oxo-2H-pyran-5-carboxylate (2c): colorless oil (167 mg, 60%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 – 8.20 (m, 1H), 7.83 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.48 – 7.34 (m, 2H), 7.10 – 6.99 (m, 2H), 5.74 (d, *J* = 4.3 Hz, 1H), 3.87 (s, 3H), 2.98 (d, *J* = 4.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ163.4, 162.7 (d, *J* = 247.1 Hz), 160.1, 156.4, 136.2, 135.9 (d, *J* = 3.2 Hz), 130.0, 128.5 (d, *J* = 8.3 Hz, 2C), 115.6 (d, *J* = 21.7 Hz, 2C), 112.3, 71.0, 52.5.; **IR** (film, cm^{-1}): 2976, 1716, 1296, 1222, 989; **HRMS** (ESI) m/z calcd for $[M+Na^+]$ $C_{14}H_{11}NaFO_5$ 301.0483, found 301.0488.

Methyl 3-((4-bromophenyl)(hydroxy)methyl)-2-oxo-2H-pyran-5-carboxylate (2d): colorless oil (185 mg, 55%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.2 Hz, 1H), 7.84 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 5.70 (s, 1H), 3.87 (s, 3H), 3.08 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.4, 160.1, 156.4, 139.2, 136.4, 131.8(2C), 129.8, 128.4(2C), 122.4, 112.3, 70.9, 52.6; **IR** (film, cm^{-1}): 2974, 2864, 1714, 1228, 1151, 989, 792; **HRMS** (ESI) m/z calcd for $[M+Na^+]$ $C_{14}H_{11}BrNaO_5$ 360.9682, found 360.9676.

Methyl 3-((2-bromophenyl) (hydroxy)methyl)-2-oxo-2H-pyran-5-carboxylate (2e): colorless oil (118 mg, 35%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 2.5, 0.4 Hz, 1H),7.62 – 7.53 (m, 2H), 7.48 (dd, *J* = 2.5, 1.0 Hz, 1H), 7.39 (td, *J* = 7.5, 1.0 Hz, 1H), 7.25 – 7.17 (m, 1H), 6.08 (d, *J* = 4.5 Hz, 1H), 3.83 (s, 3H), 3.52 (d, *J* = 4.5 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ163.4, 160.7, 156.1, 138.4, 137.6, 133.0, 129.9, 128.6, 128.5, 127.9, 122.9, 112.3, 70.5, 52.5; **IR** (film,

cm^{-1}): 2974, 1720, 1438, 1296, 1228, 1024, 945, 754; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{14}H_{11}BrNaO_5$ 360.9682, found 360.9697.

Methyl 3-((4-cyanophenyl)(hydroxy)methyl)-2-oxo-2H-pyran-5-carboxylate (2f): yellow oil (202 mg, 71%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.5 Hz, 1H), 7.89 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 5.79 (s, 1H), 3.87 (s, 3H), 3.33 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.3, 160.0, 156.7, 145.5, 136.8, 132.4(2C), 129.3, 127.4(2C), 118.5, 112.4, 112.0, 70.7, 52.6; **IR** (film, cm^{-1}): 2987, 1717, 1228, 111, 989; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{15}H_{11}NNaO_5$ 308.0529, found 308.0540.

Methyl 3-(hydroxyl (2-nitrophenyl) methyl)-2-oxo-2H-pyran-5-carboxylate (2g): colorless oil (192 mg, 63%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ8.27 (d, *J* = 2.3 Hz, 1H), 8.03 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.68 (td, *J* = 7.7, 1.2 Hz, 1H), 7.63 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.57 – 7.42 (m, 1H), 6.33 (s, 1H), 3.85 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.3, 160.2, 156.7, 148.3, 137.0, 134.8, 133.9, 129.3, 129.1, 128.7, 125.0, 112.2, 67.0, 52.5; **IR** (film, cm^{-1}): 2976, 1720, 1350, 1072 931, 835; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{14}H_{11}NNaO_5$ 328.0428, found 328.0432.

Methyl 3-(hydroxy(4- (trifluoromethyl)phenyl) methyl)-2-oxo-2H-pyran-5-carboxylate (2h): colorless oil (233 mg, 71%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.5 Hz, 1H), 7.81 (d, *J* = 2.5, Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 5.72 (s, 1H), 3.79 (s, 3H), 3.23 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ163.4, 160.1, 156.5, 144.2 (q, *J* = 1.0 Hz), 136.6, 130.50 (q, *J* = 32.5 Hz), 129.6, 127.0, 125.6 (q, *J* = 3.7 Hz), 123.96 (q, *J* = 272.2 Hz), 112.4, 70.9, 52.6; **IR** (film, cm^{-1}): 2976, 2856, 1716, 1571, 1440, 1323, 1230, 920; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{15}H_{11}F_3NaO_5$ 351.0451, found 351.0444.

Methyl 3-(hydroxy(4-methoxyphenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (2i): colorless oil (82 mg, 28%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 2.2 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.73 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.5, 160.1, 159.7, 156.2, 135.9, 132.2, 130.3, 128.1(2C), 114.1(2C), 112.3, 71.2, 55.3, 52.5; **IR** (film, cm^{-1}): 2943, 1717, 1456, 1237, 998; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{15}H_{14}NaO_6$ 313.0683, found 313.0688.

Methyl 3-(1-hydroxybutyl) -2-oxo-2H-pyran -5-carboxylate (2j): colorless oil (90 mg, 40%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 11.9, 2.5 Hz, 1H), 7.80 (dd, *J* = 2.5, 1.0 Hz, 1H), 4.63 (s, 1H), 3.89 (s, 3H), 2.53 (br, 1H), 2.11-1.87 (m, 1H), 1.84 – 1.61 (m, 1H), 1.53 – 1.22 (m, 2H), 0.96 (td, *J* = 7.4, 2.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ156.2, 156.1, 138.4, 135.9, 130.6, 127.2, 70.0, 52.5, 37.6, 18.9, 13.8; **IR** (film, cm^{-1}): 2958, 1714, 1438, 1230, 111, 960; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{11}H_{14}NaO_5$ 249.0733, found 249.0738.

Methyl 3-(1-hydroxyethyl) -2-oxo-2H- pyran-5-carboxylate (2k): colorless oil (75 mg, 38%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 2.5, 1.1 Hz, 1H), 7.76 (dd, *J* = 2.5, 1.1 Hz, 1H), 4.75 (q, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 2.61 (br, 1H), 1.44 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.6, 160.5, 156.1, 135.3, 131.4, 112.3, 65.9, 52.5, 21.6; **IR** (film, cm^{-1}): 3514, 2976, 1714, 1406, 1280., 1230, 943; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_9H_{10}NaO_5$ 221.0420, found 221.0413.

Methyl 3-(furan-2-yl (hydroxy)methyl)-2-oxo-2H-pyran-5-carboxylate(2l): yellow oil (151 mg, 61%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 – 8.22 (m, 1H), 7.92 (dd, *J* = 2.5, 1.2 Hz, 1H), 7.39 (t, *J* = 1.2 Hz, 1H), 6.36 (s, 1H), 6.36 (s, 1H), 5.77 (s, 1H), 3.89 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.4, 159.9, 156.7, 152.4, 142.8, 137.4, 127.2, 112.3, 110.6, 108.2, 65.9, 52.5; **IR** (film, cm^{-1}): 2975, 1717, 1300, 1278, 974; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{12}H_{10}NaO_6$ 273.0370, found 273.0376.

Methyl 3-((4-methylphenylsulfonamido)(phenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (2m): white solid (310 mg, 75 %); mp: 191-192°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.5 Hz, 1H), 7.75 (d, *J* = 2.5, 1H), 7.71 – 7.59 (m, 2H), 7.26 – 7.18 (m, 5H), 7.17 – 7.10 (m, 2H), 5.73 (d, *J* = 8.4 Hz, 1H), 5.36 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 2.36 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.1, 159.4, 156.5, 143.7, 138.0, 137.2, 137.0, 129.7(2C), 128.9(2C), 128.4, 127.4(2C), 126.5(2C), 126.3, 112.1, 58.3, 52.6, 21.4; **IR** (film, cm^{-1}): 3215, 1708, 1446, 1330, 1288, 1072, 981; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{21}H_{19}NNaO_6S$ 436.0825, found 436.0824.

Methyl 3-((4-methylphenylsulfonamido) (4-(trifluoromethyl) phenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (2n): white solid (405 mg, 84 %); mp: 167-168°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.4 Hz, 1H), 7.80 – 7.69 (m, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.04 (d, *J* = 9.3 Hz, 1H), 5.44 (d, *J* = 9.2 Hz, 1H), 3.89 (s, 3H), 2.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ162.9, 159.3, 156.9, 144.0, 141.1 (q, *J* = 1.1 Hz), 138.6, 137.0, 130.7, 130.5 (q, *J* = 32.6 Hz), 129.7(2C), 125.7 (q, *J* = 3.7 Hz), 125.5, 127.2(2C), 127.0(2C), 123.8 (q, *J* = 272.3 Hz) 112.1, 58.1, 52.7, 21.4; **IR** (film, cm^{-1}): 3217, 1728, 1701, 1446, 1325, 999, 815; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{22}H_{18}F_3NNaO_6S$ 504.0699, found 504.0716.

Methyl 3-((4-methylphenylsulfonamido) (4-nitrophenyl) methyl) -2-oxo-2H-pyran-5-carboxylate (2o): white solid (390 mg, 85 %); mp: 188-189°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.4 Hz, 1H), 8.14 – 8.00 (m, 2H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.10 (d, *J* = 9.5 Hz, 1H), 5.46 (d, *J* = 9.5 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.7, 159.3, 157.1, 147.7, 144.2, 144.1, 139.0, 136.9, 129.8(2C), 127.5(2C), 127.2(2C), 124.9, 123.9(2C), 112.1, 58.0, 52.8, 21.4; **IR** (film, cm^{-1}): 3219, 1697, 1521, 1340, 1238, 997, 817; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{21}H_{18}N_2NaO_8S$ 481.0676, found 481.0686.

Methyl 3-((4-cyanophenyl) (4-methylphenylsulfonamido) methyl) -2-oxo-2H-pyran-5-carboxylate (2p): white solid (395 mg, 90 %); mp: 219-220°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.4 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.04 (d, *J* = 9.4 Hz, 1H), 5.41 (d, *J* = 9.4 Hz, 1H), 3.89 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.8, 159.3, 157.0, 144.1, 142.4, 139.0, 136.9, 132.5(2C), 129.8(2C), 127.3(2C), 127.2(2C), 125.02, 118.2, 112.2, 112.1, 58.15, 52.75, 21.42; **IR** (film, cm^{-1}): 3228, 2233, 1679, 1570, 1442, 1274, 918; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{22}H_{18}N_2NaO_6S$ 461.0778, found 461.0792.

Methyl 3-((4-methylphenylsulfonamido) (2-nitrophenyl)methyl)-2-oxo-2H-pyran-5-carboxylate (2q): white solid; (298 mg, 65%)); mp: 155-156°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.4 Hz, 1H), 7.76 (dt, *J* = 9.4, 4.6 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.59 (d, *J* = 8.3 Hz, 2H),7.52 – 7.44 (m, 1H), 7.39 – 7.31 (m, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.11 (d, *J* = 9.4 Hz, 1H), 6.05 (d, *J* = 9.4 Hz, 1H), 3.81 (s, 3H), 2.28 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ162.7, 159.7, 157.0, 147.8, 143.9, 139.7, 136.8, 133.5, 131.9, 130.6, 129.7, 129.3, 127.2, 126.5, 125.1, 112.23, 54.2, 52.7, 21.4; **IR** (film, cm^{-1}): 3213, 1724.32, 1444.98, 1147.23, 975.98; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{21}H_{18}N_2NaO_8S$ 481.0676, found 481.0676.

Methyl 3-((4-methylphenylsulfonamido) (p-tolyl)methyl)-2-oxo-2H-pyran-5-carboxylate (2r): white solid (281 mg, 86 %); mp: 198-199°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 2.5 Hz, 1H), 7.76 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.10-6.90 (m, 4H), 5.69 (d, *J* = 8.2 Hz, 1H), 5.50 (d, *J* = 8.2 Hz, 1H), 3.89 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.1, 159.4, 156.5, 143.7, 138.3, 137.8, 137.0, 134.3, 129.7(2C), 129.5(2C), 127.4(2C), 126.5, 126.4(2C), 112.1, 57.9, 52.6, 21.4, 21.0; **IR** (film, cm^{-1}): 3213, 1724, 1707, 1444, 1170, 975, 817; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{22}H_{21}NNaO_6S$ 450.0982, found 450.0990.

Methyl 3-((4-methoxyphenyl) (4-methylphenylsulfonamido) methyl)-2-oxo-2H-pyran-5-carboxylate (2s): white solid (222 mg, 50 %); mp: 174-175°C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.14 (d, *J* = 2.5 Hz, 1H), 7.75 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.70 – 7.61 (m, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.63 (d, *J* = 8.0 Hz, 1H), 5.31 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 3.74 (s, 3H), 2.37 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.1, 159.6, 159.4, 156.4, 143.7, 137.6, 137.0, 129.6(2C), 129.3, 127.9(2C), 127. 4(2C), 126.6, 114.2(2C), 112.1, 57.7, 55.3, 52.6, 21.4; **IR** (film, cm^{-1}): 3199, 1705, 1508, 1288, 1035, 821; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{22}H_{21}NNaO_7S$ 466.0931, found 466.0930.

Methyl 3-((4-fluorophenyl) (4-methylphenylsulfonamido) methyl)-2-oxo-2H-pyran-5-carboxylate (2t): white solid (345 mg, 80 %); mp: 150-151°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.5 Hz, 1H), 7.72 (dd, *J* = 2.5, 0.7 Hz, 1H), 7.67 – 7.61 (m, 2H), 7.20 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.13 (dd, *J* = 8.5, 5.2 Hz, 2H), 6.92 (t, *J* = 8.6 Hz, 2H), 5.79 (d, *J* = 8.7 Hz, 1H), 5.35 (d, *J* = 8.6 Hz, 1H), 3.89 (s, 3H), 2.36 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.9, 162.5 (d, *J* = 248.0 Hz), 159.3, 156.6, 143.8, 138.1, 137.0, 133.1 (d, *J* = 3.2 Hz), 129.7(2C), 128.4 (d, *J* = 8.3 Hz, 2C), 127.3(2C), 126.1, 115.7 (d, *J* = 21.8 Hz, 2C) 112.1, 57.7, 52.6, 21.4; **IR** (film, cm^{-1}):3259, 3174, 1732, 1506, 1309, 1095, 975, 815; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{21}H_{18}FNNaO_6S$ 454.0731, found 454.0723.

Methyl 3-((4-bromophenyl) (4-methylphenylsulfonamido) methyl)-2-oxo-2H-pyran-5-carboxylate (2u): white solid (368 mg, 75 %); mp: 226-227°C; **^{1}H NMR** (400 MHz, DMSO) δ 8.76 (d, *J* = 9.6 Hz, 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 7.81 (dd, *J* = 2.5, 0.9 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.51 – 7.37 (m, 2H), 7.34 – 7.20 (m, 2H), 7.16 – 7.06 (m, 2H), 5.40 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 2.30 (s, 3H); **^{13}C NMR** (100 MHz, DMSO) δ 163.0, 159.2, 157.5, 142.9, 137.77, 137.5, 137.3, 131.2(2C), 129.4(4C), 126.5(2C), 125.6, 120.9, 111.3, 55.1, 52.3, 20.8; **IR** (film, cm^{-1}):3197, 1707, 1586, 1433, 1168, 912; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{21}H_{18}NBrNaO_6S$ 513.9930, found 513.9924.

Methyl 2-(hydroxyl (4-nitrophenyl)methyl)-[1,1'-biphenyl]-4-carboxylate (3a): To an oven dried sealed tube **2a** (304 mg 1equiv) and ethynylbenzene (140 µL, 1.5 equiv) were added, The sealed tube was purged with Ar and then stirred at 120 ^{o}C for 4 h. The crude product was direct purified by flash chromatography, afford **3a**, colorless oil (300 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 1.8 Hz, 1H), 8.12 – 8.05 (m, 2H), 8.01 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.39 – 7.32 (m, 1H), 7.31 – 7.28 (m, 1H), 7.28 – 7.24 (m, 3H), 6.08 (s, 1H), 3.92 (s, 3H), 2.53 (br, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.6, 150.5, 147.1, 145.8, 140.5, 139.5, 130.6, 130.0, 129.0, 128.9(2C), 128.6, 128.4(2C), 128.0, 127.3(2C), 123.5(2C), 71.6, 52.3; **IR** (film, cm^{-1}): 2929, 1712, 1453, 919; **HRMS** (ESI) m/z calcd for [M+H^+] $C_{21}H_{18}NO_5$ 364.1179, found 364.1177.

Methyl 3-(acetoxy(4-nitrophenyl)methyl) -2-oxo-2H-pyran-5-carboxylate (4a): yellow solid (330 mg, 95 %); mp: 96-97°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 – 8.24 (m, 1H), 8.22 – 8.07 (m, 2H), 7.92 (m, 1H), 7.78 – 7.51 (m, 2H), 6.79 (s, 1H), 3.89 (s, 3H), 2.19 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.0, 163.2, 158.6, 157.2, 148.0, 143.9, 136.8, 128.2(2C), 126.4, 123.9(2C), 112.0, 70.8, 52.7, 20.9; **IR** (film, cm^{-1}): 2958, 1714, 1230, 1101, 910; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{16}H_{13}NNaO_8$ 370.0533, found 370.0538.

Experimental procedure for the synthesis of compound 5a, 5b:

To a solution of **4a** (347 mg, 1.0 mmol), tetrabutylammonium bromide (32 mg, 0.1 mmol) and allyl alcohol or N-allyl-tosyl amine (2.0 mmol, 2 equiv) in THF (10 mL) at room temperature was added K_2CO_3 (138 mg, 1.0 mmol).

The reaction was stirred at room temperature for 15 h, then heated to 50 ^{o}C for 4 h, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography.

Methyl 1-(4-nitrophenyl)-8-oxo-3,3a,4,5-tetrahydro-1H-5,7a-(epoxymethano)isobenzofuran-6-carboxylate (5a): yellow oil (300 mg, 87 %); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 – 8.10 (m, 2H), 7.76 (m, 2H), 6.55 – 6.34 (m, 1H), 5.81 – 5.67 (m, 1H), 5.62 (s, 1H), 4.26 (m, 1H), 3.68 (s, 3H), 3.34 (m, 1H), 3.05 – 2.89 (m, 1H), 2.51 (m, 1H), 1.53 – 1.40 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ170.6, 161.7, 147.8, 145.1, 138.3, 135.7, 127.2(2C), 123.9(2C), 77.2 74.971.0, 59.4, 52.4, 42.2, 28.0; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{17}H_{15}NNaO_7$ 368.0741, found 368.0729.

Methyl 1-(4-nitrophenyl)-8-oxo-2-tosyl-1,2,3,3a,4,5-hexahydro-5,7a-(epoxymethano) isoindole-6-carboxylate (5b): white solid (334 mg, 67 %); mp: 160-161°C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 6.55 – 6.47 (m, 1H), 5.65 (dd, *J* = 3.9, 2.0 Hz, 1H), 5.46 (s, 1H), 3.94 (dd, *J* = 11.9, 7.0 Hz, 1H), 3.73 (s, 3H), 3.00 (t, *J* = 12.1 Hz, 1H), 2.47 (s, 3H), 2.32 (ddd, *J* = 14.3, 9.0, 4.7 Hz, 1H), 1.95 – 1.83 (m, 1H), 1.36 (dd, *J* = 14.3, 9.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.0, 161.4, 147.8, 145.0, 144.9, 138.0, 135.0, 133.2, 130.3(2C), 128.4(2C), 127.7(2C), 124.0(2C), 74.5, 62.6, 59.8, 53.1, 52.5, 39.4, 27.5, 21.7; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{24}H_{22}N_2NaO_8S$ 521.0989, found 512.0970.

Experimental procedure for the synthesis of compound 6a, 6b: To a solution of **5a** (300 mg, 1.0 equiv) or **5b** (334 mg, 1 equiv**)** in MeOH (1 mL) at room temperature was added MeONa 1.0 equiv. The reaction was stirred at room temperature for 2 h, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography. The reaction quenched with 1M HCl 5 mL, mixture was extracted with DCM (20 mL), and the layers were separated. The organic layer was washed with brine (10 mL), dried (MgSO4), and concentrated. The crude product was purified by flash chromatography gave the corresponding desired product **6a**, **6b**.

Dimethyl 6-hydroxy-3-(4-nitrophenyl)- 1,3,3a,6,7,7a-hexahydroisobenzofuran-3a,5-dicarboxylate (6a): colorless oil (298mg, 91%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 6.19 (s, 1H), 5.33 (s, 1H), 4.70 – 4.52 (m, 1H), 4.28 – 4.13 (m, 1H), 3.90 (dd, *J* = 8.9, 5.0 Hz, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.34 (br, 1H), 3.30 – 3.21 (m, 1H), 2.08 – 1.99 (m, 1H), 1.96 – 1.82 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ172.2, 166.4, 147.8, 144.4, 136.0, 135.2, 127.5(2C), 123.5(2C), 86.2, 71.4, 61.5, 58.1,53.3, 52.2, 39.7, 30.5; **HRMS** (ESI) m/z calcd for [M+H^+] $C_{18}H_{20}NO_8$ 378.1183, found 378.1182.

Dimethyl 6-hydroxy-3-(4-nitrophenyl)-2-tosyl-2,3,3a,6,7,7a-hexahydro-1H-isoindole-3a,5-dicarboxylate (6b): colorless oil (322mg, 91%) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 6.32 (s, 1H), 5.22 (s, 1H), 4.42 (t, *J* = 5.3 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.66 (s, 3H), 3.56 (s, 3H), 3.54 – 3.46 (m, 1H), 2.45 (s, 3H), 1.98 – 1.79 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.6, 166.1, 147.6, 145.5, 144.5, 135.3, 134.3, 132.7, 129.9(2C), 128.5(2C), 128.0(2C), 123.5(2C), 69.6, 61.3, 58.4, 53.5, 52.5, 52.4, 36.4, 30.4, 21.6; **HRMS** (ESI) m/z calcd for [M+Na^+] $C_{25}H_{26}N_2NaO_9S$ 553.1251, found 553.1254.

Acknowledgements

We thank the University Sorbonne Université (former University P. et M. Curie, UPMC) and CNRS for funding. The Fédération de Recherche (FR2769) provided technical access for analysis. L.C. thanks the China Scholarship Council (CSC) for a PhD grant. The authors express their gratitude to Justin Couetil for proofreading the manuscript.

Notes and references

1 R. R. Gowda and E. Y.-X. Chen, *Org. Chem. Front.*, 2014, **1**, 230–234.
2 T. Wang, M. W. Nolte and B. H. Shanks, *Green Chem.*, 2014, **16**, 548–572.
3 M. Nardi, P. Costanzo, A. D. Nino, M. L. D. Gioia, F. Olivito, G. Sindona and A. Procopio, *Green Chem.*, 2017, **19**, 5403–5411.
4 M. Chia, T. J. Schwartz, B. H. Shanks and J. A. Dumesic, *Green Chem.*, 2012, **14**, 1850–1853.
5 W. Fan, Y. Queneau and F. Popowycz, *Green Chem.*, 2018, **20**, 485–492.
6 F. A. Kucherov, K. I. Galkin, E. G. Gordeev and V. P. Ananikov, *Green Chem.*, 2017, **19**, 4858–4864.
7 K. I. Galkin, E. A. Krivodaeva, L. V. Romashov, S. S. Zalesskiy, V. V. Kachala, J. V. Burykina and V. P. Ananikov, *Angew. Chem. Int. Ed.*, 2016, **55**, 8338–8342.
8 P. Anastas and J. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, New York, 2000.
9 R. Beerthuis, G. Rothenberg and N. R. Shiju, *Green Chem.*, 2015, **17**, 1341–1361.
10 C. G. S. Lima, J. L. Monteiro, T. de Melo Lima, M. Weber Paixão and A. G. Corrêa, *ChemSusChem*, 2018, **11**, 25–47.
11 S. Biswas, B. Dutta, A. Mannodi-Kanakkithodi, R. Clarke, W. Song, R. Ramprasad and S. L. Suib, *Chem. Commun.*, 2017, **53**, 11751–11754.
12 P. Zhao, Y. Zhang, Y. Wang, H. Cui, F. Song, X. Sun and L. Zhang, *Green Chem.*, , DOI:10.1039/C7GC03821F.
13 W. Deng, P. Wang, B. Wang, Y. Wang, L. Yan, Y. Li, Q. Zhang, Z. Cao and Y. Wang, *Green Chem.*, 2018, **20**, 735–744.

14 J. Chen, K. Shen and Y. Li, *ChemSusChem*, 2017, **10**, 3165–3187.
15 D. (D J.) Liu and E. Y.-X. Chen, *Green Chem.*, 2014, **16**, 964–981.
16 A. Axelsson, A. Antoine-Michard and H. Sundén, *Green Chem.*, 2017, **19**, 2477–2481.
17 Y. Tao, R. Dong, I. V. Pavlidis, B. Chen and T. Tan, *Green Chem.*, 2016, **18**, 1240–1248.
18 D. Basavaiah, K. V. Rao and R. J. Reddy, *Chem. Soc. Rev.*, 2007, **36**, 1581–1588.
19 G. Masson, C. Housseman and J. Zhu, *Angew. Chem. Int. Ed.*, 2007, **46**, 4614–4628.
20 Y.-L. Liu, B.-L. Wang, J.-J. Cao, L. Chen, Y.-X. Zhang, C. Wang and J. Zhou, *J. Am. Chem. Soc.*, 2010, **132**, 15176–15178.
21 V. K. Aggarwal, S. Y. Fulford and G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.*, 2005, **44**, 1706–1708.
22 K. E. Price, S. J. Broadwater, H. M. Jung and D. T. McQuade, *Org. Lett.*, 2005, **7**, 147–150.
23 D. Basavaiah, B. S. Reddy and S. S. Badsara, *Chem. Rev.*, 2010, **110**, 5447–5674.
24 A. V. Subrahmanyam, S. Thayumanavan and G. W. Huber, *ChemSusChem*, 2010, **3**, 1158–1161.
25 J.-N. Tan, M. Ahmar and Y. Queneau, *RSC Adv.*, 2015, **5**, 69238–69242.
26 A. Corma, G. W. Huber, L. Sauvanaud and P. O'Connor, *J. Catal.*, 2007, **247**, 307–327.
27 E. M. Karp, T. R. Eaton, V. S. i Nogué, V. Vorotnikov, M. J. Biddy, E. C. D. Tan, D. G. Brandner, R. M. Cywar, R. Liu, L. P. Manker, W. E. Michener, M. Gilhespy, Z. Skoufa, M. J. Watson, O. S. Fruchey, D. R. Vardon, R. T. Gill, A. D. Bratis and G. T. Beckham, *Science*, 2017, **358**, 1307–1310.
28 A. DeVierno Kreuder, T. House-Knight, J. Whitford, E. Ponnusamy, P. Miller, N. Jesse, R. Rodenborn, S. Sayag, M. Gebel, I. Aped, I. Sharfstein, E. Manaster, I. Ergaz, A. Harris and L. Nelowet Grice, *ACS Sustain. Chem. Eng.*, 2017, **5**, 2927–2935.
29 G. A. Kraus, G. R. P. Iii, C. L. Beck, K. Palmer and A. H. Winter, *RSC Adv.*, 2013, **3**, 12721–12725.
30 G. A. Kraus and S. Wang, *RSC Adv.*, 2017, **7**, 56760–56763.
31 J. J. Lee, G. R. P. Iii, D. Mitchell, L. Kasuga and G. A. Kraus, *RSC Adv.*, 2014, **4**, 45657–45664.
32 T. Guney, J. J. Lee and G. A. Kraus, *Org. Lett.*, 2014, **16**, 1124–1127.
33 T. Pfennig, R. L. Johnson and B. H. Shanks, *Green Chem.*, 2017, **19**, 3263–3271.
34 T. Pfennig, J. M. Carraher, A. Chemburkar, R. L. Johnson, A. T. Anderson, J.-P. Tessonnier, M. Neurock and B. H. Shanks, *Green Chem.*, 2017, **19**, 4879–4888.
35 J. J. Lee and G. A. Kraus, *Green Chem.*, 2014, **16**, 2111–2116.
36 G. A. Kraus, S. Riley and T. Cordes, *Green Chem.*, 2011, **13**, 2734–2736.
37 K. Plevová, L. Chang, E. Martin, Q. Llopis, L. Dechoux and S. Thorimbert, *Adv. Synth. Catal.*, 2016, **358**, 3293–3297.
38 L. Chang, K. Plevová, S. Thorimbert and L. Dechoux, *J. Org. Chem.*, 2017, **82**, 5499–5505.
39 L. Chang, N. Klipfel, L. Dechoux and S. Thorimbert, *Green Chem.*, 2018, **20**, 1491–1498.
40 M. Chia, M. A. Haider, G. Pollock, G. A. Kraus, M. Neurock and J. A. Dumesic, *J. Am. Chem. Soc.*, 2013, **135**, 5699–5708.
41 see also X. Gao, M. Xia, C. Yuan, L. Zhou, W. Sun, C. Li, B. Wu, D. Zhu, C. Zhang, B. Zheng, D. Wang and H. Guo, *ACS Catal.*, 2019, **9** 1645-1654
42 L. Dian, H. Zhao, D. Zhang-Negrerie and Y. Du, *Adv. Synth. Catal.*, 2016, **358**, 2422–2426.
43 B. Niu, W. Zhao, Y. Ding, Z. Bian, C. U. Pittman, A. Zhou and H. Ge, *J. Org. Chem.*, 2015, **80**, 7251–7257.
44 S.-L. Zhou, L.-N. Guo and X.-H. Duan, *Eur. J. Org. Chem.*, 2014, **2014**, 8094–8100.
45 During the final writing of this manuscript, Zhu reported the cross-vinylogous Rauhut-Currier reaction of methyl coumalate with enals. Q. Liu and L. Zu, *Angew. Chem. Int. Ed.*, 2018, **57**, 9505–9509.
46 When Benzaldehyde was used as substrate instead of p-nitrobenzaldehyde no reaction occurred in the absence of Lewis base.
47 N. E. Hall and B. J. Smith, *J. Phys. Chem. A*, 1998, **102**, 3985–3990.
48 R. E. Plata and D. Singleton *J. Am. Chem. Soc.*, 2015, **137**, 3811-3826.
49 S. R. Vasudevan, J. B. Moore, Y. Schymura and G. C. Churchill, *J. Med. Chem.*, 2012, **55**, 7054–7060.
50 T. David Bateman, A. L. Joshi, K. Moon, E. N. Galitovskaya, M. Upreti, T. C. Chambers and M. C. McIntosh, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6898–6901.
51 G. A. Molander, D. J. St. Jean and J. Haas, *J. Am. Chem. Soc.*, 2004, **126**, 1642–1643.
52 M. J. Campbell and J. S. Johnson, *J. Am. Chem. Soc.*, 2009, **131**, 10370–10371.
53 M. T. Crimmins and J. M. Ellis, *J. Am. Chem. Soc.*, 2005, **127**, 17200–17201.
54 G. Mariaule, S. De Cesco, F. Airaghi, J. Kurian, P. Schiavini, S. Rocheleau, I. Huskić, K. Auclair, A. Mittermaier and N. Moitessier, *J. Med. Chem.*, 2016, **59**, 4221–4234.
55 A. J. Kassick, J. Jiang, J. Bunda, D. Wilson, J. Bao, H. Lu, P. Lin, R. G. Ball, G. A. Doss, X. Tong, K.-L. C. Tsao, H. Wang, G. Chicchi, B. Karanam, R. Tschirret-Guth, K. Samuel, D. F. Hora, S. Kumar, M. Madeira, W. Eng, R. Hargreaves, M. Purcell, L. Gantert, J. Cook, R. J. DeVita and S. G. Mills, *J. Med. Chem.*, 2013, **56**, 5940–5948.
56 M. D. Meyer, R. J. Altenbach, F. Z. Basha, W. A. Carroll, S. Condon, S. W. Elmore, J. F. Kerwin, K. B. Sippy, K. Tietje, M. D. Wendt, A. A. Hancock, M. E. Brune, S. A. Buckner and I. Drizin, *J. Med. Chem.*, 2000, **43**, 1586–1603.
57 E. Giraud, C. Luttmann, F. Lavelle, J.-F. Riou, P. Mailliet and A. Laoui, *J. Med. Chem.*, 2000, **43**, 1807–1816.
58 J. Jiang, J. L. Bunda, G. A. Doss, G. G. Chicchi, M. M. Kurtz, K.-L. C. Tsao, X. Tong, S. Zheng, A. Upthagrove, K. Samuel, R. Tschirret-Guth, S. Kumar, A. Wheeldon, E. J. Carlson, R. Hargreaves, D. Burns, T. Hamill, C. Ryan, S. M. Krause, W. Eng, R. J. DeVita and S. G. Mills, *J. Med. Chem.*, 2009, **52**, 3039–3046.