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A novel enzymatic tandem process: utilization of biocatalytic promiscuity for high stereoselective synthesis of 5-hydroxyimino-4,5-dihydrofurans

Ming-Yu Wu [a], Kun Li [a,*], Ting He [a], Xing-Wen Feng [a], Na Wang [a], Xiao-Yan Wang [b], Xiao-Qi Yu [a,*]

[a] Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China
[b] Analytical and Testing Center, Sichuan University, Chengdu 610064, PR China

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ABSTRACT

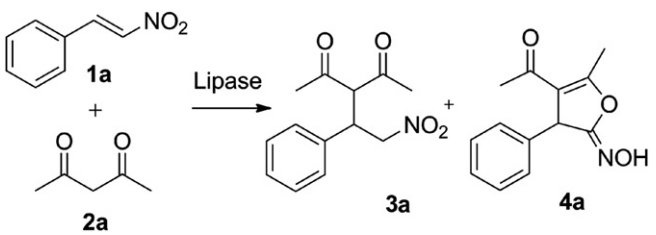
A lipase-catalyzed protocol for the synthesis of 5-hydroxyimino-4,5-dihydrofurans via tandem coupling between β-nitrostyrenes and 1,3-dicarbonyl compounds was developed in a 'one-pot' strategy. A series of β-nitrostyrenes were employed to expand the scope of this new biocatalytic promiscuity with high stereoselectivity (*Z*/*E* up to 99:1) and moderate to good yields. The reaction activity of 1,3-cyclohexanedione was found to be better than linear 2,4-pentanedione, while ethyl acetoacetate and diethylmalonate were not suitable for this reaction under the same conditions. Single-crystal X-ray diffraction analysis indicated that the reaction was stereoselective and *Z*-stereomer was found to be the major product. A reaction mechanism was supposed to elucidate the biocatalytic process.

1. Introduction

Dihydrofuran derivatives have been considered as important synthetic intermediates for their existence in a wide range of biologically active synthetics and natural products.[1] Explorations of facile and green methods for the preparation of these functionalized heterocycles received considerable attentions in synthetic organic chemistry.[2] Among these methods, tandem catalysis provide the opportunities to improve such transformations because of its atom economy and simple operation.[3] Although several metal-catalyzed tandem processes were developed,[4] there is significant interest in developing environmental friendly metal-free methods for the preparation of dihydrofuran derivatives. Further more, oxime compounds often show satisfactory insecticidal, fungicidal or herbicidal activity,[5] and the synthesis of dihydrofuran oxime derivatives were seldom reported.[6] Therefore, finding an efficient process for the preparation of such bioactive oxime-functionalized dihydrofuran derivatives is of great importance.

As an efficient and green tool for modern organic synthesis, biocatalysis has attracted increased attention for its usually excellent selectivity and mild conditions.[7] Many enzymatic tandem processes based on chemo-enzymatic reactions have been well presented.[8] However, to our knowledge, single enzymatic tandem processes, which utilize only one type of enzyme in the absence of any other chemical catalysts, is extremely scarce. As one of the most rapidly growing areas in enzymology, biocatalytic promiscuity not only highlights the existing catalysts, but provides novel and practical synthetic pathways, which are not currently available.[9] Nevertheless, the utilization of biocatalytic promiscuity of lipase in the synthesis of heterocycles was seldom reported. Herein, we wish to report a single lipase-catalyzed approach for the synthesis of 5-hydroxyimino-4,5-dihydrofurans via a tandem process with the utilization of biocatalytic promiscuity.

The lipase-catalyzed aldol, Mannich, and decarboxylative Knoevenagel reactions were systematically studied in our group previously.[10] As the successive work, our initial efforts focused on the biocatalytic promiscuity in lipase-catalyzed Michael addition between nitrostyrene and acetylacetone. But to our surprise, under the regular reaction conditions, except the routine Michael addition product **3a**, cyclic product **4a** was obtained in comparable yield to that of **3a** (Scheme 1). For the potential as fungicidal or herbicidal



Scheme 1. Lipase-catalyzed reaction of nitrostyrene and acetylacetone.

* Corresponding authors. Tel.: +86 28 85460576; fax: +86 28 85415886; e-mail address: xqyu@tfol.com (X.-Q. Yu).

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agent of the oxime,[5] product **4a** was chosen to be the target product in the novel lipase-catalyzed process.

2. Results and discussion

With the aim to get **4a** in more efficient manner, the catalytic activities of several lipases were firstly tested in mixed ethanol/water solvents. As shown in Table 1, poor yields for **3a** and **4a** were obtained in the absence of lipase (entry 12). Among the tested lipases, lipase from porcine pancreas (PPL) showed the best activity, and the yield of **4a** was 37.5%, which almost equaled that of **3a**. Meanwhile, other lipases, such as CCL, CRL, PCL, MJL, and PRL exhibited slight lower catalytic activity than PPL. As a widespread and inexpensive lipase, PPL was chosen as the biocatalyst in the following experiments.

Table 1
The catalytic activities of different lipases[a]

Entry	Enzyme	Yield **4a**[b] (%)	Yield **3a**[b] (%)
1	Lipase from porcine pancreas (PPL)	37.5	38.9
2	Lipase from *C. cylindracea* (CCL)	31.6	36.4
3	Lipase from *C. rugosa* (CRL)	34.5	38.5
4	Lipase from *P. camemberti* (PCL)	33.2	38.3
5	Lipase from *M. javanicus* (MJL)	32.9	40.2
6	Lipase from *P. roqueforti* (PRL)	32.1	32.3
7	Lipase from *R. oryzae* (ROL)	28.3	34.6
8	Lipase from *M. miehei* (MML)	28.2	37.3
9	Lipase from *P. fluorescens* (PFL)	24.7	25.3
10	Lipase from *C. antarctica* (CAL-B)	23.3	33.6
11	Denatured PPL[c]	5.4	2.8
12[c]	No enzyme	4.3	3.6

[a] Reaction performed on 0.1 mmol scale in 1 mL of EtOH/H_2O (4: 1, v/v), 50 °C, 24 h.
[b] Yields were determined by HPLC.
[c] Pre-treated with urea at 60 °C for 12 h.

Solvents are auxiliary materials in biochemical synthesis and productions, and they always play an important role in the biocatalytic process. Some commonly used solvents or mixed solvents were screened subsequently for higher yield of **4a**. Generally, as shown in Fig. 1, the reactions gave moderate yields in the mixture of polar solvents and water (DMSO/H_2O or EtOH/H_2O), while poor yields were obtained in the mixture of some aprotic solvents and water (THF/H_2O and acetone/H_2O). Without the use of water, various solvents could give different results. In the reactions using DMSO or ethanol as solvents, poor yields of **4a** but high yields of **3a** were observed. Meanwhile, no reaction was detected when using THF or acetone as solvent. In the reactions studied above, **3a** was always obtained with higher yield than the desired product **4a**. Therefore, our subsequent studies were carried out for the improvement of the reaction selectivity toward **4a** in DMSO/H_2O media.

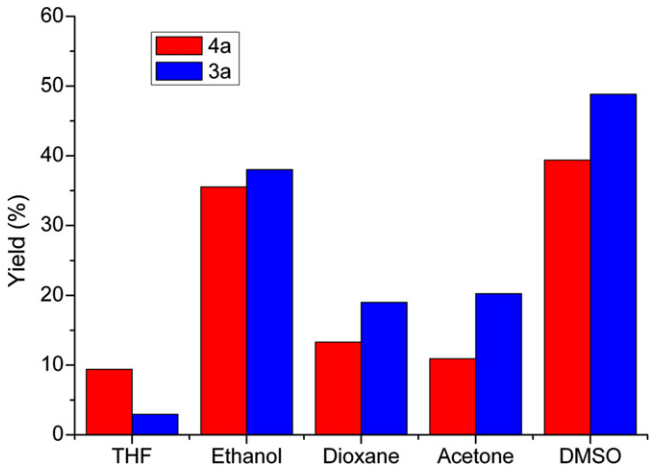


Fig. 1. The influence of mixed solvents on the tandem reaction (24 h). The solvents given in the figure indicate that the reaction was carried out in mixed solvents with the given solvent/water volume ratio of 4:1.

Our previous studies suggested that the content of water in reaction mixture could largely influence the results of biocatalytic reactions.[10] Experiments were performed to ascertain the catalytic activity of PPL with different amounts of water in the reaction system, and the results were listed in Table 2. The yield of **4a** was evidently improved to 50.3% when the content of water increased to 40% (entry 4). Further increase of water led to the decrease of yield, which could be attributed to the lower solubility of the substrates.

Table 2
The influence of different water content on the reaction[a]

Entry	Water content (%)	Yield of **4a**[b] (%)
1	5	25.6
2	10	28.9
3	20	39.4
4	40	50.3
5	60	32.2
6	80	33.9

[a] Reactions were performed for 24 h in DMSO/H_2O system.
[b] Yields were determined by HPLC.

To obtain more information of this lipase-catalyzed tandem reaction, we investigated the time course of the reaction. As shown in Fig. 2, the yields of both **3a** and **4a** increased at first 12 h, indicating that the formation of **3a** and **4a** might be two competing reactions. Time extension of the reaction led to gradually decrease of **3a** along with the increase of **4a**, suggesting that **3a** could be transformed to **4a** under the reaction conditions. The result also indicated that the Michael adduct might be the intermediate in this tandem reaction. The yield of **4a** reached to a relatively high plateau of about 60% in 36 h. According to the results, subsequent reactions were carried out for 48 h.

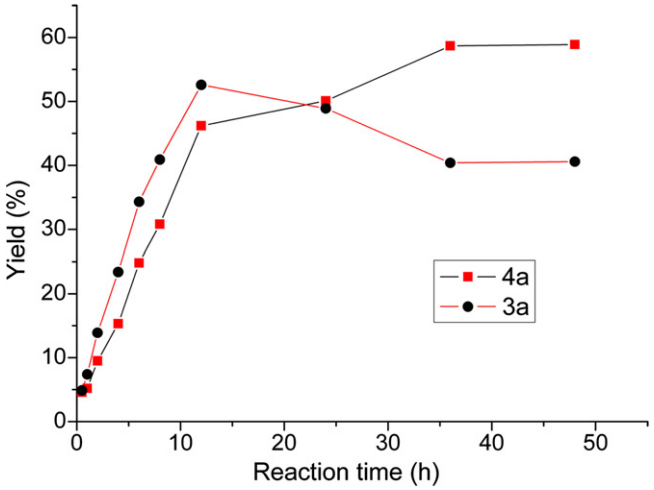
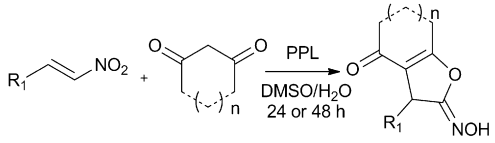
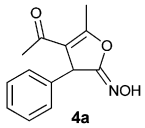
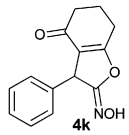
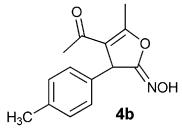
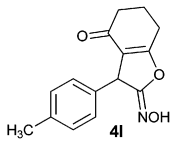
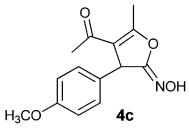
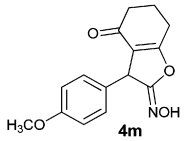
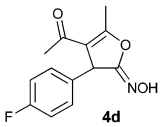
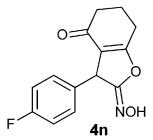
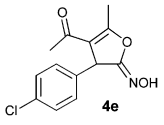
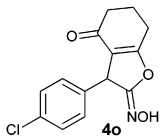
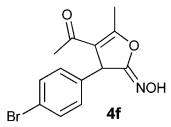
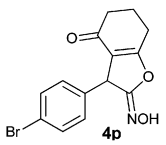
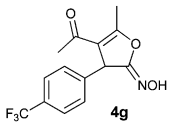
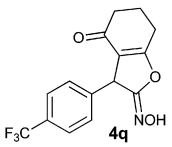
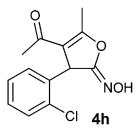
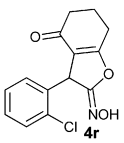
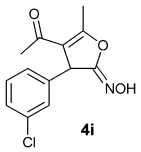
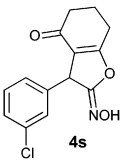
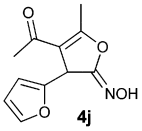


Fig. 2. The content of **3a** and **4a** in the reaction system at different time (determined by HPLC).

A range of β-nitrostyrenes and 1,3-diones were then surveyed to expand the scope of this new biocatalytic promiscuity in the one-pot tandem reaction. As shown in Tables 3 and 2, 4-pentanedione (n=0) and 1,3-cyclohexanedione (n=1) were used as 1,3-dione substrates. It was found that a wide range of β-nitrostyrenes could effectively participate in this reaction and gave desired products **4** with moderate to good yields (50–86%). Electronic effect of substituents on phenyl ring of β-nitrostyrenes did not seem to influence the yield, and *o*-chloro-β-nitrostyrene (entries 8 and 18)

Table 3
Synthesis of 5-hydroxyimino-4,5-dihydrofurans with different β-nitrostyrene and 2,4-pentanedione or 1,3-cyclohexanedione[a]



Entry	R_1	n	Product **4**	Yield[b] (%)	Z/E[c]	Entry	R_1	n	Product **4**	Yield[b] (%)	Z/E[c]
1	C_6H_5	0	 **4a**	61.7	>99:1	11	C_6H_5	1	 **4k**	64.3	>99:1
2	4-$CH_3C_6H_4$	0	 **4b**	51.4	>99:1	12	4-$CH_3C_6H_4$	1	 **4l**	54.6	71:29
3	4-$CH_3OC_6H_4$	0	 **4c**	63.6	>99:1	13	4-$CH_3OC_6H_4$	1	 **4m**	73.8	>99:1
4	4-FC_6H_4	0	 **4d**	48.9	>99:1	14	4-FC_6H_4	1	 **4n**	63.5	91:9
5	4-ClC_6H_4	0	 **4e**	50.6	>99:1	15	4-ClC_6H_4	1	 **4o**	70.8	65:35
6	4-BrC_6H_4	0	 **4f**	50.7	>99:1	16	4-BrC_6H_4	1	 **4p**	61.2	64:36
7	4-$CF_3C_6H_4$	0	 **4g**	52.3	96:4	17	4-$CF_3C_6H_4$	1	 **4q**	65.4	46:54
8	2-ClC_6H_4	0	 **4h**	80.6	>99:1	18	2-ClC_6H_4	1	 **4r**	85.7	28:72
9	3-ClC_6H_4	0	 **4i**	54.5	97:3	19	3-ClC_6H_4	1	 **4s**	65.6	>99:1
10	C_4H_3O	0	 **4j**	51.4	>99:1						

[a] The reaction was conducted with 200 mg PPL, 2 mmol of nitrostyrene, 4 mmol of 2,4-pentanedione or 1,3-cyclohexanedione in 20 mL of DMSO/H_2O mixture (3:2, v/v) at 50 °C for 24 h (entries 11–19) or 48 h (entries 1–10).
[b] Isolated yield.
[c] Z/E Ratio was determined by ^1H NMR.

gave the highest yield of 85.7%. According to the single-crystal X-ray diffraction analysis of products **4a** and **4k** (Fig. 3), we could confirm that the reaction gave the product oximes with *Z*-stereoselectivity. ^{1}H NMR showed that high *Z*/*E* selectivities (up to >99%) were obtained in the reaction products. Further, the results also indicated that the reaction activity of 1,3-cyclohexanedione (entries 11–19) was better than that of linear 2,4-pentanedione (entries 1–10). However, 2,4-pentanedione always gives better stereoselectivity. Other diones, such as 1,3-cyclopentanedione, ethyl acetoacetate, and diethylmalonate could not give products **4** under such conditions (data not shown). Detailed information revealed that only Michael product was found for 1,3-cyclopentanedione, while ethyl acetoacetate and diethylmalonate would hydrolyze by lipase and therefore could not react smoothly. In the absence of lipase, low yield of **4a** (about 15%) was obtained. The rise of reaction temperature to 80 °C led to more unsatisfactory result, indicating that lipase was indispensable for good yield of product **4**. Compared with the reaction catalyzed by NEt_3 in methanol[6c], much less by-product of dihydrofuran with the nitro group leaving[11] was produced, thus obtained good stereoselectivity (*Z*/*E* up to 99:1) and extensive substrates.

3. Conclusion

In conclusion, we have developed a tandem process for preparing 5-hydroxyimino-4,5-dihydrofurans and 2,3,6,7-tetrahydrobenzofurans via the reaction between β-nitrostyrene and 1,3-dicarbonyl compounds with the utilization of biocatalytic promiscuity under mild conditions. The starting materials are commercially available or can be easily prepared. We believe that these results can not only highlight the biocatalytic promiscuity but also afford a facile access to functionalized dihydrofurans and their derivatives.

4. Experimental

4.1. Materials and general methods

Lipase from porcine pancreas (PPL), Lipase from *Candida antarctica* (CAL-B), lipase from *Candida cylindracea* (CCL), lipase from *Mucor javanicus* (MJL), lipase from *Candida rugosa* (CRL) and lipase from *Rhizopus oryzae* (ROL) were purchased from Sigma. Lipase from *Mucor miehei* (MML) and lipase from *Penicillium camemberti*

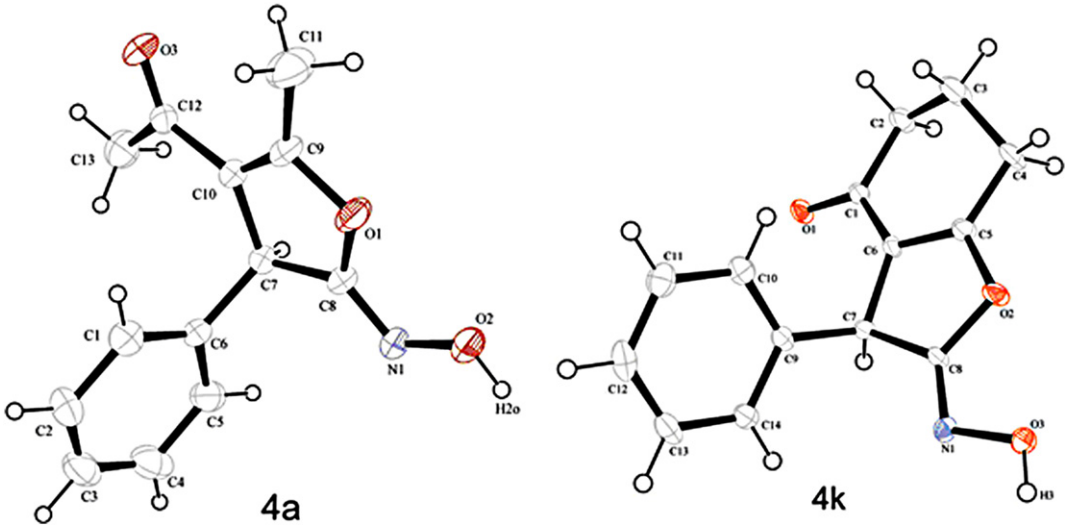


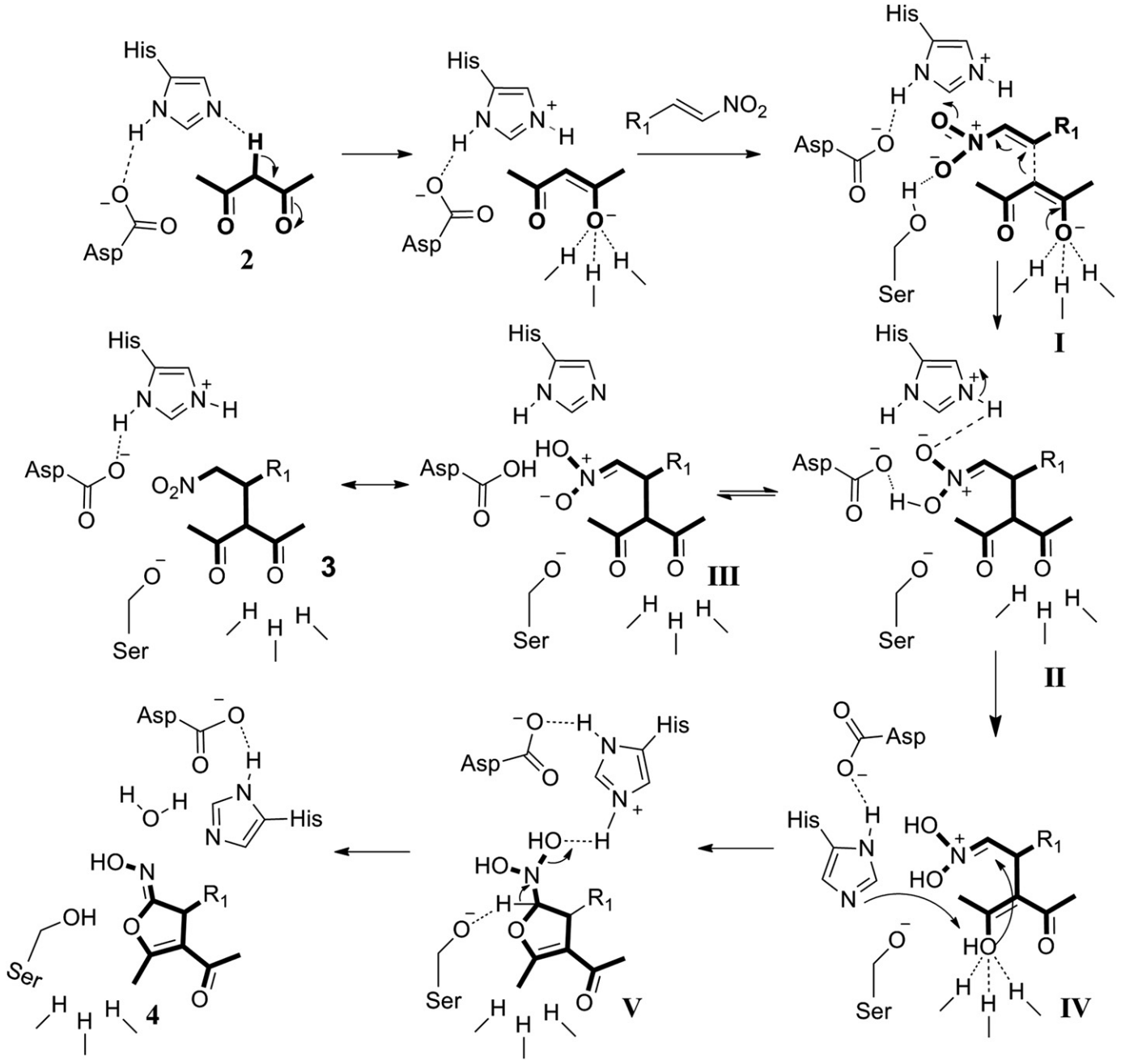
Fig. 3. Structures of **4a** and **4k** characterized by single-crystal X-ray diffraction.[12]

It is widely accepted that the hydrolysis site in hydrolase is still responsible for its promiscuous catalysis.[13] Combining such viewpoint with the observations in this study, we proposed the mechanism of this lipase-catalyzed tandem reaction, which was described in Scheme 2. Firstly, β-nitrostyrene and 1,3-dicarbonyl compounds were activated, respectively, by the serine residue and oxyanion hole of the lipases.[14] Then intermediate **II** was generated from enolate anion (**I**) and β-nitrostyrene with the assistance of Asp-His dyad. **II** could be transformed to **III** (another form of **3**) or **IV** (which is the enolate of the **III** on the carbonyl group) easily. Next, the intermediate **IV** could be activated by his and oxyanion hole, and then formation of **V** via an intramolecular cyclization. Further elimination of a water molecule gave the product **4**. That is to say, there are two reaction routes for intermediate **II**: (a) protonation to give compound **3** in a slow reversible reaction, and (b) cyclization of the enolate of **III** on the dicarbonyl moiety to give **4**. Based on the mechanism from above and the experiment that compound **3** could be gradually transformed to **4** when increasing the reaction time, we can see that **4** was more stable than **3** under the reaction condition. Further experiments are now in progress to prove this hypothesis.

(PCL) were purchased from Fluka. Lipase from *Pseudomonas fluorescens* (PFL), and lipase from *Penicillium roqueforti* (PRL) are a gift from the Amano Enzyme China Ltd. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument using $CDCl_3$ and DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS; the coupling constants *J* are given in hertz. HPLC was carried out using a Shimadzu organizer consisting of an LC-2010A HT Integrator, a UV/vIS Detector. C18 column was used in the HPLC experiments with methanol/water=50:50 (v/v), 0.8 mL/min and UV=254 nm. HRMS were performed on Bruker Daltonics Bio TOF mass spectrometer. 1,3-Cyclohexanedione and 2,4-pentanedione were purchased from Aladdin Reagent Company. Column chromatography was performed using EM Silica gel (300–400 mesh).

4.2. Typical experimental procedure for synthesis of nitrostyrene

Aryl aldehyde (0.05 mol), nitromethane (0.05 mol), and MeOH (10–20 mL) were added in round-bottom flask and then stirred vigorously. 10 mL of 10.5 mol/L NaOH solution was added



Scheme 2. Proposed mechanism of lipase-catalyzed tandem reaction.

dropwise in an ice bath, a larger number of white or yellow solid would precipitated, stirring continued for 15 min. Distilled water was added until the solution became clear, then the solution was added dropwise to 30 mL concentrated HCl and yellow solid would precipitated. The yellow solid were filtered and washed with water, then evaporation under vacuum drying oven. After recrystallization from ethanol, yellow needle-like crystalloid was obtained.

4.3. Typical experimental procedure for synthesis of 5-hydroxyimino-4,5-dihydrofurans

Nitrostyrene (2 mmol), 1.3-dicarbonyl compounds (4 mmol), 200 mg PPL, 12 mL DMSO, and 8 mL water were added in a 50 mL round-bottom flask. The mixture was stirred at 50 °C for 24 h or 48 h, filtrated to get rid of the enzyme (PPL), then 25 mL brine was added and the solution was extracted with ethyl acetate (50 mL) for three times. The organic phase was combined and wished with brine (25 mL), then dried (Na_2SO_4), filtered, and evaporated in vacuum. The residue was purified by flash column chromatography from 5:1 to 2:1 (petroleum ether: ethyl acetate), and compounds **3** as well as **4** were separated, respectively.

*4.3.1. 3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (**3a**).* White solid; ^{1}H NMR (400 MHz, TMS, $CDCl_3$): δ 7.35–7.29 (m, 3H, Ph–H), 7.20–7.17 (m, 2H, Ph–H), 4.63 (dd, 2H, J=3.2, 5.2 Hz, $-CH_2$), 4.37 (d, 1H, J=10.8 Hz, –CH), 4.27–4.21 (m, 1H, –CH), 2.30 (s, 3H, $-CH_3$), 1.94 (s, 3H, $-CH_3$); ^{13}C NMR (100, MHz, $CDCl_3$): 201.8, 201.0, 136.0, 129.4, 128.6, 127.9, 78.2, 70.8, 42.8, 30.4, 29.5. ESIMS: 272.1 $[M+Na]^+$.

*4.3.2. 1-(5-(Hydroxyimino)-2-methyl-4-phenyl-4,5-dihydrofuran-3-yl)ethanone (**4a**).* White solid; mp 140–142 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 7.48 (s, 1H, −OH), 7.36–7.27 (m, 3H, Ph−H), 7.19–7.17 (m, 2H, Ph−H), 4.90 (d, 1H, *J*=2 Hz, −CH), 2.51 (d, 3H, *J*=1.6 Hz, $-CH_3$), 1.97 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 193.9, 164.2, 157.9, 138.2, 129.3, 128.1, 127.5, 117.6, 49.3, 29.8, 14.3. HRMS (ESI) calcd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0968; found: 232.0974.

*4.3.3. 1-(5-(Hydroxyimino)-2-methyl-4-(p-tolyl)-4,5-dihydrofuran-3-yl)ethanone (**4b**).* White solid; mp 134–136 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H, −OH), 7.13 (d, 2H, *J*=8.0 Hz, Ph−H), 7.06 (d, 2H, *J*=8.0 Hz, Ph−H), 4.86 (q, 1H, *J*=1.6 Hz, −CH), 2.50 (d, 3H, *J*=1.6 Hz, $-CH_3$), 2.31 (s, 3H, Ph−CH_3), 1.96 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 194.1, 164.1, 158.1, 137.9, 135.1, 129.9, 127.3, 117.6, 49.0, 29.8, 21.1, 14.3. HRMS (ESI) calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125; found: 246.1131.

*4.3.4. 1-(5-(Hydroxyimino)-4-(4-methoxyphenyl)-2-methyl-4,5-dihydrofuran-3-yl)ethanone (**4c**).* White solid; mp 144–146 °C; ^1H NMR (400 MHz, $CDCl_3$): δ. 7.15 (d, 2H, *J*=8.8 Hz, Ph−H), 6.84 (d, 2H, *J*=8.8 Hz, Ph−H), 6.62 (s, 1H, −OH), 4. 88 (d, 1H, *J*=2 Hz, −CH), 3.79 (s, 3H, $-OCH_3$), 2.52 (d, 3H, *J*=1.6 Hz, $-CH_3$), 1.99 (s, 1H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 193.9, 163.8, 159.3, 158.3, 130.2, 128.6, 117.7, 114.7, 55.3, 48.6, 29.8, 14.3. HRMS (ESI) calcd for $C_{14}H_{16}NO_4$ $[M+H]^+$: 262.1074; found: 262.1078.

*4.3.5. 1-(4-(4-Fluorophenyl)-5-(hydroxyimino)-2-methyl-4,5-dihydrofuran-3-yl)ethanone (**4d**).* White solid; mp 138–140 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H, −OH), 7.17–7.14 (m, 2H, Ph−H), 7.04–6.99 (m, 2H, Ph−H), 4.90 (d, 1H, *J*=1.6 Hz, −CH), 2.50 (d, 3H, *J*=2.0 Hz, $-CH_3$), 2.01 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 193.5, 163.9, 161.1, 157.6, 134.1, 129.2, 129.1, 117.8, 116.2, 116.0, 48.6, 29.7, 14.4. HRMS (ESI) calcd for $C_{13}H_{13}FNO_3$ $[M+H]^+$: 250.0874; found: 250.0879.

*4.3.6. 1-(4-(4-Chlorophenyl)-5-(hydroxyimino)-2-methyl-4,5-dihydrofuran-3-yl)ethanone (**4e**).* White solid; mp 139–141°C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 1H, −OH), 7.41 (d, 2H, *J*=8.4 Hz, Ph−H), 7.24 (d, 2H, *J*=8.4 Hz, Ph−H), 5.12 (d, 1H, *J*=1.6 Hz, −CH), 2.45 (d, 3H, *J*=1.6 Hz, $-CH_3$), 2.03 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 192.8, 163.8, 155.4, 138.9, 131.9, 129.4, 128.7, 117.4, 47.3, 29.6, 14.2. HRMS (ESI) calcd for $C_{13}H_{13}ClNO_3$ $[M+H]^+$: 266.0578; found: 266.0579.

*4.3.7. 1-(4-(4-Bromophenyl)-5-(hydroxyimino)-2-methyl-4,5-dihydrofuran-3-yl)ethanone (**4f**).* White solid; mp 140–143 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 1H, −OH), 7.54 (d, 2H, *J*=8.4 Hz, Ph−H), 7.18 (d, 2H, *J*=8.4 Hz, Ph−H), 5.11 (d, 1H, *J*=1.2 Hz, −CH), 2.45 (d, 3H, *J*=1.2 Hz, $-CH_3$), 2.03 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.3, 164.3, 155.8, 139.9, 132.1, 130.2, 120.9, 117.9, 47.9, 30.1, 14.7. HRMS (ESI) calcd for $C_{13}H_{13}BrNO_3$ $[M+H]^+$: 310.0073; found 310.0077.

*4.3.8. 1-(5-(Hydroxyimino)-2-methyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydrofuran-3-yl)ethanone (**4g**).* White solid; mp 140–141 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.32 (s, 1H, −OH), 7.71 (d, 2H, *J*=8.4 Hz, Ph−H), 7.45 (d, 2H, *J*=8.4 Hz, Ph−H), 5.23 (d, 1H, *J*=1.6 Hz, −CH), 2.47 (d, 3H, *J*=1.2 Hz, $-CH_3$), 2.07 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.1, 164.6, 155.6, 145.1, 128.9, 126.1, 126.0, 118.0, 48.2, 30.1, 14.8. HRMS (ESI) calcd for $C_{14}H_{13}F_3NO_3$ $[M+H]^+$: 300.0842; found: 300.0854.

*4.3.9. 1-(4-(2-Chlorophenyl)-5-(hydroxyimino)-2-methyl-4,5-dihydrofuran-3-yl)ethanone (**4h**).* White solid; mp 148–150 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.28 (s, 1H, −OH), 7.47–7.44 (m, 1H, Ph−H), 7.32–7.25 (m, 3H, Ph−H), 5.45 (s, 1H, −CH), 2.45 (d, 3H, *J*=1.2 Hz, $-CH_3$), 2.02 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.0, 164.5, 155.2, 137.5, 133.1, 130.3, 129.6, 128.1, 117.5, 47.5, 29.8, 14.7. HRMS (ESI) calcd for $C_{13}H_{13}ClNO_3$ $[M+H]^+$: 266.0578; found: 266.0579.

*4.3.10. 1-(4-(3-Chlorophenyl)-5-(hydroxyimino)-2-methyl-4,5-dihydrofuran-3-yl)ethanone (**4i**).* White solid; mp 147–150 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.33 (10.12) (s, 1H, −OH), 7.39–7.33 (m, 2H, Ph−H), 7.30–7.16 (m, 2H, Ph−H), 5.14 (5.27) (d, 1H, *J*=1.6 Hz, −CH), 2.46 (d, 3H, *J*=2.0 Hz, $-CH_3$), 2.06 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.3, 164.6, 155.7, 142.8, 133.7, 131.1, 127.9, 127.8, 126.7, 117.7, 48.0, 30.1, 14.8. HRMS (ESI) calcd for $C_{13}H_{13}ClNO_3$ $[M+H]^+$: 266.0578; found: 266.0579.

*4.3.11. 1-(2′-(Hydroxyimino)-5′-methyl-2′,3′-dihydro-[2,3′-bifuran]-4′-yl)ethanone (**4j**).* White solid; mp 130–132 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H, −OH), 7.84(s, 1H, Ar−H), 7.17 (d, 1H, *J*=3.6 Hz, Ar−H), 6.63 (q, 1H, *J*=1.6 Hz, Ar−H), 6.31 (s, 1H, −CH), 2.40 (s, 3H, $-CH_3$), 1.51 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): 201.5, 166.9, 150.3, 145.6, 145.5, 120.6, 113.2, 112.5, 86.0, 32.2, 25.4. HRMS (ESI) calcd for $C_{11}H_{11}NO_4Na$ $[M+Na]^+$: 244.0580; found: 244.0579.

*4.3.12. 2-(Hydroxyimino)-3-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4k**).* White solid; mp 159–161 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H, −OH), 7.30–7.18 (m, 5H, Ph−H), 4.99 (s, 1H, −CH), 2.81–2.63 (m, 2H, $-CH_2$), 2.27–2.24 (m, 2H, $-CH_2$), 2.06–1.99 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): 192.9, 174.2, 165.4, 136.9, 128.6, 128.4, 127.3, 118.2, 44.9, 36.9, 22.9, 21.4. ESIMS: 266.2 $[M+Na]^+$.

*4.3.13. 2-(Hydroxyimino)-3-(p-tolyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4l**).* White solid; mp 150–152 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (7.20) (s, 1H, −OH), 7.14–7.09 (m, 4H, Ph−H), 4.85 (5.10, s) (t, 1H, *J*=2.0 Hz, −CH), 2.83–2.66 (m, 2H, $-CH_2$), 2.44–2.32 (m, 2H, $-CH_2$), 2.30 (s, 3H, $-CH_3$), 2.20–2.11 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 193.6 (193.1), 172.7 (172.9), 158.4, 137.4 (137.1), 134.4 (132.3), 129.6 (129.3), 127.4 (127.7), 118.4 (119.2), 45.6 (45.0), 36.9 (36.8), 23.1, 21.3, 21.1 (21.1). ESIMS: 280.1 $[M+Na]^+$.

*4.3.14. 2-(Hydroxyimino)-3-(4-methoxyphenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4m**).* White solid; mp 158–159 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H, −OH), 7.15 (d, 2H, *J*=8.8 Hz, Ph−H), 6.84 (d, 2H, *J*=8.8 Hz, Ph−H), 4.85 (5.10) (s, 1H, −CH), 3.77 (s, 3H, $-OCH_3$), 2.80–2.65 (m, 2H, $-CH_2$), 2.46–2.35 (m, 2H, $-CH_2$), 2.20–2.13 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$): 193.5, 172.6, 159.0, 158.2, 129.7, 128.9, 128.6, 118.4, 114.2, 114.0, 55.3, 45.2, 36.9, 23.1, 21.3. ESIMS: 296.1 $[M+Na]^+$.

*4.3.15. 3-(4-Fluorophenyl)-2-(hydroxyimino)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4n**).* White solid; mp 146–148 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.46 (10.24) (s, 1H, −OH), 7.29–7.20 (m, 2H, Ph−H), 7.17–7.07 (m, 2H, Ph−H), 4.93 (5.03) (s, 1H, −CH), 2.81–2.64 (m, 2H, $-CH_2$), 2.55–2.24 (m, 2H, $-CH_2$), 2.13–2.02 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.5, 174.1, 163.0, 156.5, 135.5 (J_{CF}=3 Hz), 130.0, 129.9, 117.1, 115.7, 115.5, 44.5, 36.9, 23.0, 21.4. HRMS (ESI) calcd for $C_{14}H_{13}FNO_3$ $[M+H]^+$: 262.0874; found: 262.0883.

*4.3.16. 3-(4-Chlorophenyl)-2-(hydroxyimino)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4o**).* White solid; mp 156–158 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 10.50 (10.28) (s, 1H, −OH), 7.37 (7.34) (d, 2H, *J*=8.4 Hz, Ph−H), 7.23 (7.27) (d, 2H, *J*=8.4 Hz, Ph−H), 4.95 (5.04) (s, 1H, −CH), 2.81–2.63 (m, 2H, $-CH_2$), 2.3–4-2.31 (m, 2H, $-CH_2$), 2.11–2.00 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.5 (192.9), 174.3 (174.4), 165.0 (156.3), 138.4 (135.9), 132.2

(131.9), 130.0 (130.3), 128.6 (128.8), 117.8 (116.9), 44.7 (44.3), 36. 9 (36.8), 23.0 (22.9), 21.4 (21.3). ESIMS: 300.0 $[M+Na]^+$.

*4.3.17. 3-(4-Bromophenyl)-2-(hydroxyimino)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4p**).* White solid; mp 170–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.32 (10.27) (s, 1H, –OH), 7.52–7.46 (m, 2H, Ph–H), 7.22–7.16 (m, 2H, Ph–H), 4.93 (5.02) (s, 1H, –CH), 2.81–2.63 (m, 2H, $-CH_2$), 2.32–2.23 (m, 2H, $-CH_2$), 2.12–2.01 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.5 (192.9), 174.3 (172.4), 156.2 (165.0), 138.8 (136.4), 131.8 (131.5), 130.3 (130.7), 120.7 (120.4), 116.9 (117.8), 44.7 (44.4), 36.9 (36.8), 23.0 (23.0), 21.4 (21.3). HRMS (ESI) calcd for $C_{14}H_{13}BrNO_3$ $[M+H]^+$: 322.0073; found: 322.0070.

*4.3.18. 2-(Hydroxyimino)-3-(4-(trifluoromethyl)phenyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4q**).* White solid; mp 154–156 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.32 (10.54) (s, 1H, –OH), 7.65 (d, 2H, J=8.0 Hz, Ph–H) (7.68, d, J=8.4 Hz), 7.49 (d, 2H, J=8.0 Hz, Ph–H) (7.45, d, J=8.4 Hz), 5.08 (5.16) (s, 1H, –CH), 2.83–2.66 (m, 2H, $-CH_2$), 2.34–2.24 (m, 2H, $-CH_2$), 2.13–2.01(m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.2 (192.9), 174.6 (174.5), 164.9 (156.0), 144.0 (141.7), 129.4, 129.0, 125.8, 125.7, 125.6, 125.5, 117.7 (116. 8), 45.1 (44.8), 36.9 (36.8), 23.0 (22.9), 21.4 (21.3). HRMS (ESI) calcd for $C_{15}H_{13}F_3NO_3$ $[M+H]^+$: 312.0842; found: 312.0845.

*4.3.19. 3-(2-Chlorophenyl)-2-(hydroxyimino)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4r**).* White solid; mp 146–148 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.46 (10.16) (s, 1H, –OH), 7.44–7.21 (m, 4H, Ph–H), 5.24 (5.32) (s, 1H, –CH), 2.81–2.64 (m, 2H, $-CH_2$), 2.31–2.21 (m, 2H, $-CH_2$), 2.12–2.01 (m, 2H, $-CH_2$); ^{13}C NMR (100 MHz, DMSO-d_6): 193.2 (192.6), 174.5 (174.6), 155.7, 136.5 (133.1), 130.1 (129.7), 129.4, (129.0), 127.8 (127.7), 116.3, 44.5, 36.8, 23.1 (23.0), 21.4 (21.4). HRMS (ESI) calcd for $C_{14}H_{13}ClNO_3$ $[M+H]^+$: 278.0578; found: 278.0583.

*4.3.20. 3-(3-Chlorophenyl)-2-(hydroxyimino)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (**4s**).* White solid; mp 154–156 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (s, 1H, –OH), 7.32–7.26 (m, 3H, Ph–H), 7.23–7.19 (m, 1H, Ph–H), 5.07 (s, 1H, –CH), 2.81–2.62 (m, 2H, $-CH_2$), 2.26 (t, 2H, J=1.6 Hz, $-CH_2$), 2.06–1.99 (m, 2H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 192.9, 174.6, 164.9, 139.3, 133.2, 130.5, 128.4, 127.4, 127.1, 117.6, 44.5, 36.8, 23.0, 21.4. HRMS (ESI) calcd for $C_{14}H_{13}ClNO_3$ $[M+H]^+$: 278.0578; found: 278.0583.

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Supplementary data

Supplementary data include ^{1}H and ^{13}C NMR spectra of the target compounds described in this article. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.01.060. These data include MOL file and InChiKey of the most important compound described in this article.

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12. Compound **4a**: $C_{13}H_{13}O_3$, M=231.24, T=292 (2) K, wavelength=0.71073 Å, monoclinic, space group P 21/n, a=10.905 (3) Å, b=9.222 (3) Å, c=11.873 (4) Å, α=90°, β=95.10(2)°, γ=90°, V=1189.4 (6) Å^3, Z=4, Dc=1.291 mg cm^{-3}, μ=0.092 mm^{-1}, F(000)=488, crystal size 0.40×0.38 × 0.18 mm^3, theta range for data collection 2.43–25.53°, independent reflections 2212 [R(int)=0.0107], reflections collected 2480, refinement method full-matrix least-squares on F^2, goodness-of-fit on F^2 1.043, final R indices [$I>2\sigma(I)$], R_1=0.0637, wR_2=0.1155, R indices (all data) R_1=0.1528, wR_2=0.1324, extinction coefficient 0.0095 (18), largest diff. peak and hole 0.184 and −0.174 e Å^{-3}. **4k**: $C_{14}H_{13}O_3$, M=243.25, T=113 (2) K, wavelength=0.71073 Å, monoclinic, space group C2/c, a=20.188 (15) Å, b=7.184 (5) Å, c=17.027 (12) Å, α=90°, β=101.062 (2)°, γ=90°, V=2424 (3) Å^3, Z=8, Dc=1.333 mg cm^{-3}, μ=0.094 mm^{-1}, F(000)=1024, crystal size 0.20×0.12×0.10 mm^3, theta range for data collection 2.06–25.02°, reflections collected/unique 7781/2136 [R(int)=0.0557], refinement method full-matrix least-squares on F^2, goodness-of-fit on F^2 1.

043, final R indices [$I>2\sigma(I)$], R_1=0.0560, wR_2=0.1424, R indices (all data) R_1=0.0693, wR_2=0.1493, largest diff. peak and hole 0.184 and −0.174 e Å^{-3}. CCDC 769655 (**4a**) and 769656 (**4k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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