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# A novel and efficient direct aldol condensation from ketones and aromatic aldehydes catalyzed by proline–TEA through a new pathway

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ABSTRACT

A novel and efficient direct aldol condensation from various ketones and a wide range of aldehydes was catalyzed by L-proline–TEA (triethylamine) in MeOH at room temperature, affording the corresponding (*E*)-α,β-unsaturated ketones in excellent yields. By using the method, some complicated (*E*)-α,β-unsaturated ketone C-glycosides were obtained from unmodified ketone C-glycosides and aldehydes. This reaction proceeds through a new pathway, in which the specific intermediate was captured and identified.



## 1. Introduction

Acyclic or cyclic α,β-unsaturated carbonyl compounds have been reported to be potentially important structural characteristics in small molecule drugs used to prevent or treat cancer.[1] They are also versatile organic molecules used frequently as substrates for carbonyl addition, conjugate addition, and the Morita–Baylis–Hillman reaction.[2]

C-Glycosides as subunits occur in a variety of biologically important natural products and synthetic compounds. Flavone C-glycoside,[3a] β-C-glycoside analogs of KRN7000,[3b] and fagomine C-glycoside[3c] have been reported to exhibit antitumor, antibacterial, antiviral, and glycosidase inhibitory activities (Fig. 1).[3d] Therefore, development of new routes for the synthesis of C-glycosides has attracted much attention. Ketone C-glycosides **1** (Fig. 2) have been synthesized conveniently for many years.[4] However, further modification of **1** is very limited.[5] Thus, we are interested in transforming the ketone C-glycosides **1** into α,β-unsaturated ketone C-glycosides **2** (Fig. 2), which should be useful precursors for achieving new biologically active C-glycoside derivatives.

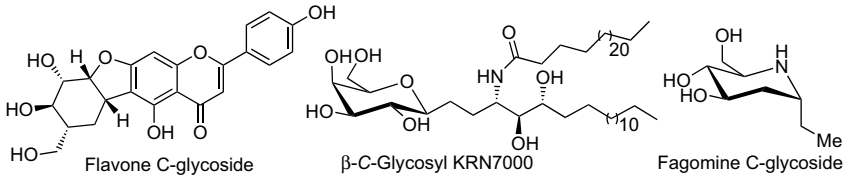
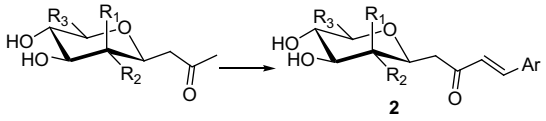



**Figure 1.** C-Glycosides with biological activities.



**1a** $R_1$= H $R_2$ = OH $R_3$ = $CH_2OH$ **1b** $R_1$= OH $R_2$ = H $R_3$ = $CH_2OH$
**1c** $R_1$= H $R_2$ = OH $R_3$ = H

**Figure 2.** Unmodified ketone C-glycosides **1** and (*E*)-α,β-unsaturated ketone C-glycosides **2**.

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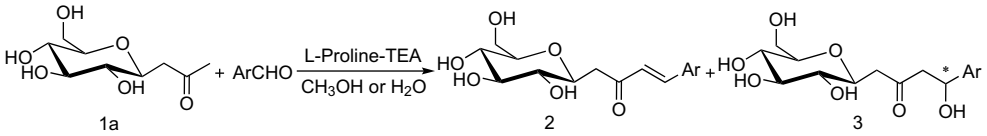
**Table 1**
Aldol and aldol condensation reactions of ketone C-glycoside **1a** with aldehydes




| Entry | ArCHO | Media | Time (h) | **2** Yield[a] (%) | **3** Yield (%)/(de %)[b] |
|---|---|---|---|---|---|
| 1 | *p*-$NO_2$PhCHO | $H_2O$ | 72 | **2a** (—) | **3a** (60/39) |
| 2 | *p*-$NO_2$PhCHO | MeOH | 72 | **2a** (trace) | **3a** (73/20) |
| 3 | Piperonal | $H_2O$ | 24 | **2b** (—) | **3b** (0/—) |
| 4 | Piperonal | MeOH | 24 | **2b** (98) | **3b** (0/—) |

[a] Isolated yields.
[b] The de values were determined by chiral HPLC analysis.

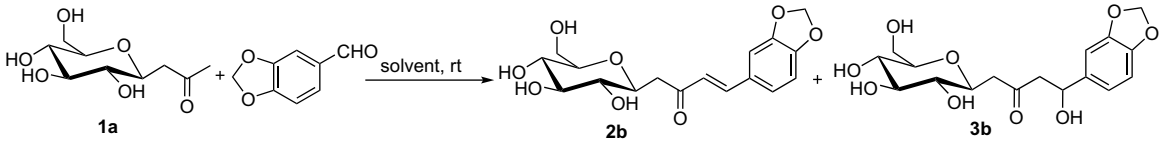
Normally, α,β-unsaturated carbonyl compounds are prepared from aromatic aldehydes and ketones by Claisen–Schmidt condensation under strong basic conditions,[6] which suffer from several side reactions and narrow substrate diversity. Mild Lewis acid-catalyzed tandem Mukaiyama aldol–dehydration reactions have been described, but require pre-formation of enolates from ketones.[7] Many researchers have tried to optimize the reaction conditions to the direction of aldol condensation between alhehydes and/or ketones.[8] However, the reaction always produces mixed products. Recently, Wang[9] and co-workers reported a novel pyrrolidine imide-catalyzed aldol condensation from ketones and aldehydes, with moderate to good yields in DMSO (41–95%). Unfortunately, the ketone substrates were limited to acetone and cyclopentanone, and reactions with other ketone substrates proceeded very slowly, with low yields.[9] Moreover, we found that the method is also not feasible for the synthesis of (*E*)-α,β-unsaturated ketone C-glycosides. Here we report a novel, simple, mild method for the preparation of (*E*)-α,β-unsaturated compounds, which is applicable to a wide range of ketones and aldehydes. It is particularly efficient for the preparation of (*E*)-α,β-unsaturated ketone C-glycosides from unmodified ketone C-glycosides.

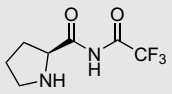
## 2. Results and discussion

Based on our recent work indicating that dipeptide-organobases could efficiently catalyze the direct aldol reactions of ketones and aldehydes in water,[10] coupled with our wish to utilize 'green chemistry' methods, we were interested in studying the aldol reactions between aldehydes and ketone C-glycosides in water, expecting to achieve some meaningful chiral C-glycoside derivatives **3**.

We first examined the aldol reaction between ketone C-glycoside **1a** and 4-nitro-benzaldehyde in the presence of 20 mol % L-proline–TEA at room temperature in water. The desired aldol product **3a** was obtained only in 60% yield, with 39% de (Table 1, entry 1). Even using methanol as solvent, the yield and enantioselectivity did not improve significantly (Table 1, entry 2). However, using piperonal instead of 4-nitro-benzaldehyde, the aldol condensation product **2a** was obtained unexpectedly in 98% yield in methanol, although the reaction did not take place in water (Table 1, entries 3 and 4). This unexpected result diverted our interest to explore the efficient synthetic procedure for the (*E*)-α,β-unsaturated ketone C-glycosides **2**.

**Table 2**
Catalyst screening for the aldol condensation reaction




| Entry | Catalyst[a] | Time (h) | Yield (%)[b] for product **2b** | Yield (%)[b] for product **3b** |
|---|---|---|---|---|
| 1 | Proline | 72 | — | 0 |
| 2 | Pro–Trp | 72 | — | 0 |
| 3[c] |  | 72 | Trace | 0 |
| 4 | Proline–TEA | 24 | 98 | 0 |
| 5 | Trp-OH-TEA | 72 | 54 | 0 |
| 6 | Phe-OH-TEA | 72 | 60 | 0 |
| 7 | Leu-OH-TEA | 72 | 43 | 0 |
| 8 | Pro-Trp-TEA | 72 | Trace | 0 |
| 9 | Pro-Leu-TEA | 72 | Trace | 0 |
| 10 | HOAc–TEA | 72 | — | 0 |
| 11 | TEA or DABCO | 72 | — | 0 |
| 12 | Proline–DABCO | 26 | 97 | 0 |
| 13 | Proline–piperazine | 25 | 98 | 0 |
| 14 | Proline–$Me_2CHNH_2$ | 22 | 97 | 0 |
| 15 | Proline–AcONa | 72 | — | 0 |
| 16 | Proline–$Na_2CO_3$ | 72 | — | 0 |

[a] Unless otherwise indicated, all the reactions were carried out in MeOH and the loading of organocatalyst was 20 mol %.
[b] Isolated yields.
[c] The reaction was conducted in DMSO or in MeOH.

**Table 3**
Solvent screening for the aldol condensation reaction

| Entry | Solvent | Time (h) | Yield[a] (%) for **2b** | Yield[a] (%) for **3b** |
|---|---|---|---|---|
| 1 | MeOH | 24 | 98 | 0 |
| 2 | EtOH | 72 | 90 | 0 |
| 3 | *i*-PrOH | 72 | 85 | 0 |
| 4 | $CH_3CN$ | 120 | — | 0 |
| 5 | THF | 120 | — | 0 |
| 6 | DMSO | 120 | Trace | 0 |
| 7 | DMF | 120 | Trace | 0 |
| 8 | $CHCl_3$ | 120 | — | 0 |
| 9 | $PhCH_3$ | 120 | — | 0 |

[a] Isolated yields.

**Table 4**
Effect of proline and TEA loading on the aldol condensation reaction

| Entry | Proline loading (mol %) | TEA loading (mol %) | Time (h) | Yield[a] (%) for product **2b** |
|---|---|---|---|---|
| 1 | 5 | 5 | 120 | 30 |
| 2 | 10 | 10 | 72 | 92 |
| 3 | 15 | 15 | 38 | 94 |
| 4 | 15 | 30 | 28 | 98 |
| 5 | 15 | 60 | 27 | 98 |
| 6 | 15 | 90 | 27 | 97 |

[a] Isolated yields.

Accordingly, a series of acid-base catalysts, including amino acids, dipeptides, simple organic bases, and their combination, were screened for the aldol condensation reaction of ketone C-glycoside **1a** with piperonal in methanol at room temperature, and the results are listed in Table 2.

Neither proline nor Pro–Trp,[10] efficient organocatalysts for general aldol reactions, showed any catalytic activity (Table 2, entries 1 and 2). Using the reported pyrrolidine imide, an efficient catalyst for the aldol condensation reaction,[9] only trace amount of product was produced in DMSO or MeOH (Table 2, entry 3). However, the combination of the commercially available amino acids with triethylamine (TEA) could significantly catalyze the reaction, affording the aldol condensation products **2a** in moderate to excellent yields (Table 2, entries 4–7). Especially, when proline–TEA was used as the catalyst, the yield increased remarkably to 98%. The catalytic effect of Pro-Trp-TEA and Pro-Leu-TEA was also examined, but only a trace amount of the desired product was obtained (Table 2, entries 8 and 9). Furthermore, catalyst AcOH–TEA and TEA did not show any catalytic activity (Table 2, entries 10 and 11). Combinations of proline with various bases were also screened. Organobases, such as DABCO, piperazine, and isopropylamine were as effective as TEA (Table 2, entries 12–14), while inorganic bases did not show any catalytic effect (Table 2, entries 15–16). Therefore, the proline–TEA should be a suitable acid–base catalyst for this reaction.

Subsequently, the effect of different solvents on the reaction was studied in the presence of 20 mol % proline–TEA, under the same conditions (Table 3). We found that high yield was achieved in alcohol (Table 3, entries 1–3). In contrast, only trace or no product was observed in other organic solvents. Comparatively, MeOH was considered as the most suitable solvent for its high efficiency, low price, and easy handling.

The reaction of **1a** with piperonal was then used as the model, and the loading amount of proline and TEA was evaluated for their effect on the reaction efficiency (Table 4). The yield increased from 30% to 94% by increasing proline–TEA loading from 5 mol % to 15 mol %, and the reaction time was also reduced greatly from 120 h to 38 h (Table 4, entries 1–3). At a constant proline loading of 15 mol %, a little higher loading of TEA could enhance the reaction efficiency (Table 4, entry 4), while a further increase of TEA did not improve significantly the reaction (Table 4, entries 5 and 6). Thus, the combination of 15 mol % of proline and 30 mol % of TEA was optimal to ensure high reaction efficiency while maintaining a reasonable reaction time.

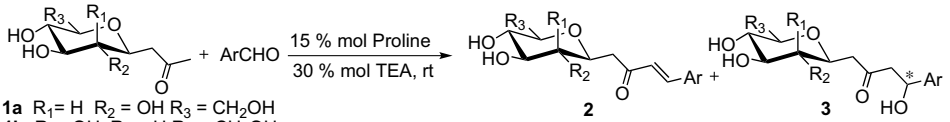
The generality of the reaction was then examined under the optimal reaction conditions, namely using 15 mol % of L-proline and 30 mol % of TEA as catalyst, methanol as solvent and reaction at room temperature. As shown in Table 5, all reactions proceeded smoothly, affording the corresponding (*E*)-α,β-unsaturated ketones **2** in excellent yields, except entry 18. It is clear that the reaction was applicable to quite a wide scope of aldehydes, including heteroaromatic aldehydes and aromatic aldehydes with moderate electron-withdrawing and electron-donating groups. Meanwhile, it is effective not only for the hexose-derivatized ketone glycosides (**1a** and **1b**), but also for the pentose-derivatized ketone glycoside (**1c**).

To further extend the substrate scope, the reactions of piperanol with other unmodified simple ketones were also explored (Table 6). Amazingly, all the reactions resulted in α,β-unsaturated compounds without the observation of aldol products as well. Furthermore, we found that tandem aldol condensation reactions took place easily for the symmetric cyclic ketones especially for cyclohexanone (Table 6, entries 4 and 5). Obviously, the reaction is a universal method for the formation of α,β-unsaturated carbonyl compounds, and is applicable to a wide scope of ketone substrates, including cyclic/acyclic alkyl ketones and aryl ketones.

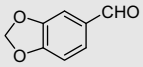
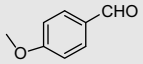
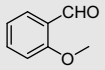
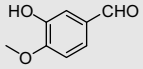
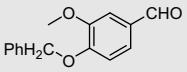
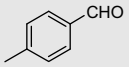
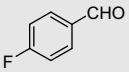
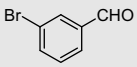
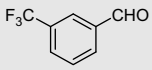
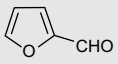
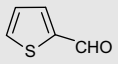
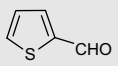
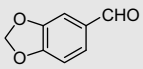
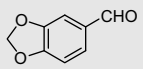
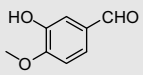
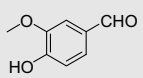
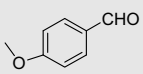
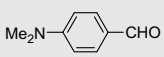
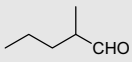
Generally, the formation of (*E*)-α,β-unsaturated carbonyl compounds catalyzed by proline was proposed to be carried out via the enamine mechanism **A**[11] or the imine mechanism **B**[9,12] (Scheme 1). Initially, we also thought that the mechanism **A** should be acceptable, because the reaction between **1a** and *p*-$NO_2$PhCHO provided an aldol product instead of an aldol condensation product (Table 1, entry 2). In order to verify the mechanism with solid evidence, we tried to capture the key intermediate. The corresponding intermediate of the reaction between **1a** and 4-methoxybenzaldehyde (Table 5, entry 2) was captured carefully by preparative TLC ($CH_3OH$, $R_f$=0.50). It was unexpectedly found, however, that the structure of the intermediate captured was a three-component conjugated intramolecular salt **VIc**, which was identified by $^1$H NMR and ESI-TOF$^+$ spectra. On the basis of the experimental results, we propose a new reaction pathway **C**. An asymmetric aldol reaction first takes place via an enamine, forming the β-hydroxy-enamine **III**, which then undergoes a dehydration process to afford a novel intermediate **VI**. After the leaving of proline, the α,β-unsaturated ketone C-glycoside **2** is generated.

The experimental results are explained readily according to this newly proposed pathway. Due to the low energy of the three-component conjugated intermediate **VI**, the formation of α,β-unsaturated ketone C-glycosides **2** is easier than the formation of the aldol product **3.** For aldehydes bearing strong electron-withdrawing groups, it is unfavorable for the dehydration of β-hydroxy-enamine intermediate **III** to form the intermediate **VI**, which led to the aldol products with high yield (Table 1, entry 2). On the contrary, for aldehydes with strong electron-donating groups, such as *p*-$Me_2$N-PhCHO (Table 5, entry 18), the intermediate **VI** is not only formed easily, but is also quite stable, making the reaction stop at this stage even at room temperature. Therefore, when 110 mol % of proline was used, we could obtain the pure intermediate **VIs** in 90% overall yield at room temperature within an hour (Scheme 2). And when **VIs** was heated in methanol, the corresponding (*E*)-α,β-unsaturated ketone C-glycoside **2s** was also formed in 60% yield. These results further supported the pathway **C**. In the proposed route C, the easy formation of the intermediate **VI** from **III** might derived from the low energy of the conjugated system **VI**, which also result in the difficulty for the leaving of proline from the ketoimine **VI**. And it is certain that the formation of **VI** must be assisted by a base catalyst such as TEA, for only proline could not catalyze the

**Table 5**
Aldol condensation reactions of ketone C-glycosides and aldehydes

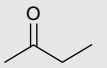
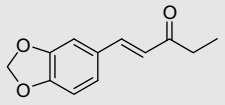
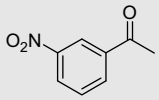
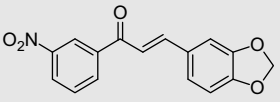
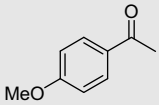
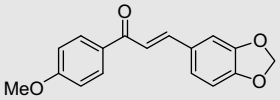
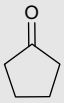
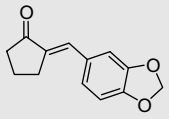
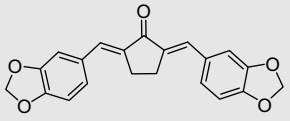
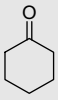
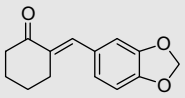
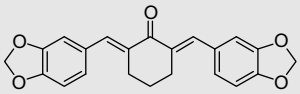



**1a** $R_1$= H $R_2$ = OH $R_3$ = $CH_2OH$
**1b** $R_1$= OH $R_2$ = H $R_3$ = $CH_2OH$
**1c** $R_1$= H $R_2$ = OH $R_3$ = H

| Entry | Ketones | Aldehydes | Time (h) | Yield[a] (%) for Product **2b–2t** | |
|---|---|---|---|---|---|
| 1 | **1a** |  | 28 | **2b** | 98 |
| 2 | **1a** |  | 27 | **2c** | 96 |
| 3 | **1a** |  | 30 | **2d** | 99 |
| 4 | **1a** |  | 29 | **2e** | 95 |
| 5 | **1a** |  | 29 | **2f** | 94 |
| 6 | **1a** |  | 26 | **2g** | 97 |
| 7 | **1a** |  | 20 | **2h** | 91 |
| 8 | **1a** |  | 19 | **2i** | 97 |
| 9 | **1a** |  | 21 | **2j** | 96 |
| 10 | **1a** |  | 28 | **2k** | 90 |
| 11 | **1a** |  | 28 | **2l** | 92 |
| 12 | **1b** |  | 28 | **2m** | 90 |
| 13 | **1b** |  | 29 | **2n** | 92 |
| 14 | **1c** |  | 27 | **2o** | 97 |
| 15 | **1c** |  | 29 | **2p** | 95 |
| 16 | **1c** |  | 29 | **2q** | 95 |
| 17 | **1c** |  | 28 | **2r** | 98 |
| 18 | **1a** |  | 72<br>10[b] | **2s** | 10<br>60[b] |
| 19 | **1a** |  | 72 | **2t** | — |

[a] Isolated yields.
[b] The reaction was conducted at reflux.

**Table 6**
Aldol condensation reactions of various ketones and piperonal

| Entry | Ketone | Time (h) | Product (**2u**–**2yb**) | Yield[a] (%) |
|---|---|---|---|---|
| 1 |  | 26 |  (**2u**) | 92 |
| 2 |  | 20 |  (**2v**) | 94 |
| 3 |  | 82 |  (**2w**) | 80 |
| 4 |  | 29 |  (**2xa**) | 85 |
| | | |  (**2xb**) | 9 |
| 5 |  | 29 |  (**2ya**) | 36 |
| | | |  (**2yb**) | 55 |

[a] Isolated yield. The products were isolated by filtration and silica gel chromatography.

reaction (Table 2, entry 1). All the phenomena indicate that the leaving of proline must be the determining step of the reaction, which also explains why an excess amount of base is favorable for the reaction.

## 3. Conclusions

In conclusion, we have developed an efficient method for the synthesis of (*E*)-α,β-unsaturated ketones from direct aldol condensation, catalyzed by proline–TEA in methanol. This method has the advantages of a wide scope of substrates, mild reaction conditions, simple work-up, and high yield. This method has been used successfully in the synthesis of (*E*)-α,β-unsaturated ketone C-glycosides, providing a potential application for the synthesis of C-glycoside derivatives.

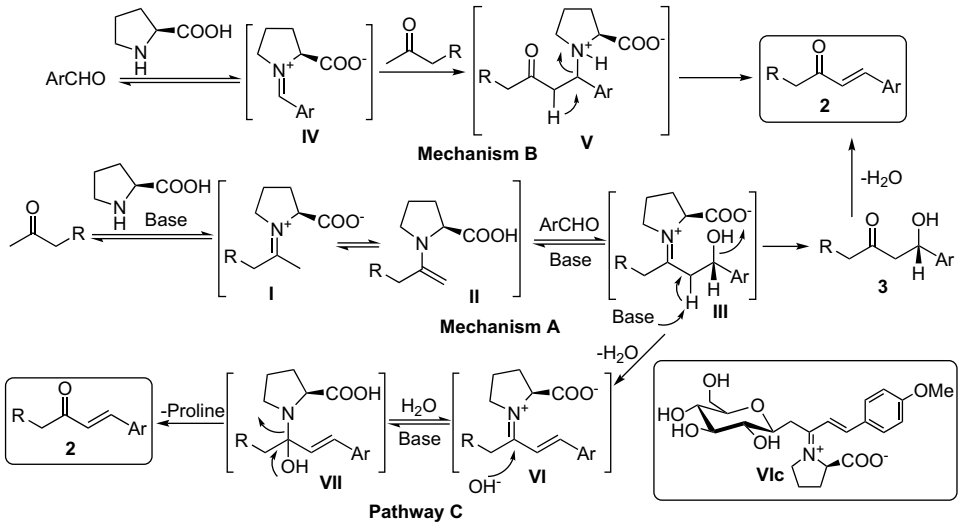
## 4. Experimental

### 4.1. General procedure for the synthesis of 2 and 3a

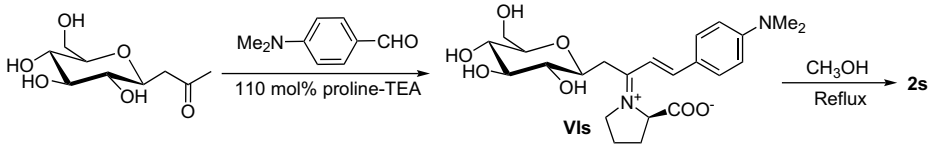
A mixture of compound **1** (0.5 mmol), an aldehyde (0.6 mmol), and proline (0.075 mmol)–TEA (0.15 mmol) in 1.0 mL of anhydrous $CH_3OH$ was stirred at room temperature for 19–30 h. The endpoint of the reaction was monitored by TLC. The resulting mixture was purified by filtration and/or silica gel chromatography and fractions were collected and concentrated in vacuo to provide a solid or clear oil **2** and **3a**. The de values of **3a** were determined by HPLC analysis with a Chiralpak AS-H column, 25% isopropyl alcohol in hexane, 1.0 mL/min, 254 nm, retention times minor 11.9 min, major 17.5 min.

*4.1.1. (E)-4-(Benzo[d][1,3]dioxol-5-yl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2b**)*

Obtained in 98% yield; white powder; mp: 150–152 °C; $^1$H NMR (300 MHz, $D_2O$): δ 7.47 (d, *J*=16.2 Hz, 1H), 7.05 (s, 1H) overlapping with 7.04–7.00 (d, *J*=8.4 Hz, 1H), 6.75 (d, *J*=8.4 Hz, 1H), 6.57 (d, *J*=16.2 Hz, 1H), 5.86 (s, 2H), 3.66–3.62 (m, 2H), 3.51–3.47 (m, 1H), 3.32 (m, 1H), 3.22 (m, 2H), 3.14–2.99 (m, 2H), 2.77 (dd, *J*=9.0,




**Scheme 1.** Proposed mechanisms for the aldol condensation process catalyzed by proline–TEA.




**Scheme 2.** Synthesis of the intermediate **VIs** and product **2s**.

15.5 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 197.9, 149.4, 148.1, 142.1, 128.9, 125.3, 124.9, 108.6, 106.7, 101.6, 80.7, 78.1, 75.8, 73.6, 70.3, 61.1, 43.3. Anal. Calcd for $C_{17}H_{20}O_8$: C 57.95, H 5.72; found: C 57.83, H 5.74.

*4.1.2. (E)-4-(4-Methoxyphenyl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2c**)*

Obtained in 96% yield; white powder; mp: 152–154 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.68 (d, $J$=8.7 Hz, 2H), 7.56 (d, $J$=16.2 Hz, 1H), 6.99 (d, $J$=8.7 Hz, 2H), 6.82 (d, $J$=16.2 Hz, 1H), 5.06 (d, $J$=6.0 Hz, 1H), 4.94 (d, $J$=4.5 Hz, 1H), 4.87 (d, $J$=4.5 Hz, 1H), 4.36 (t, $J$=5.4 Hz, 1H), 3.80 (s, 3H), 3.64–3.56 (m, 2H), 3.40–3.36 (m, 1H), 3.18–3.16 (m, 1H), 3.08–3.07 (m, 2H), 2.98–2.89 (m, 2H), 2.77 (dd, $J$=8.4, 16.2 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 197.9, 161.1, 142.0, 130.4, 130.3, 127.1, 124.6, 114.5, 114.4, 80.7, 78.2, 75.9, 73.6, 70.3, 61.1, 55.4, 43.2. Anal. Calcd for $C_{17}H_{22}O_7$: C 60.35, H 6.55; found: C 60.32, H 6.55.

*4.1.3. (E)-4-(2-Methoxyphenyl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2d**)*

Obtained in 99% yield; colorless oil; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.77 (d, $J$=16.2 Hz, 1H), 7.71 (d, $J$=7.8 Hz, 1H), 7.43–7.38 (m, 1H), 7.08 (d, $J$=7.8 Hz, 1H), 7.00–6.95 (m, 1H) overlapping with 6.95 (d, $J$=16.2 Hz, 1H), 5.09 (d, $J$=5.4 Hz, 1H), 4.98 (d, $J$=3.6 Hz, 1H), 4.90 (d, $J$=3.9 Hz, 1H), 4.36 (t, $J$=5.4 Hz, 1H), 3.86 (s, 3H), 3.63–3.54 (m, 2H), 3.40–3.36 (m, 1H), 3.16–3.14 (m, 1H), 3.11–3.05 (m, 2H), 2.96–2.90 (m, 2H), 2.72 (dd, $J$=8.7, 16.2 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 198.0, 158.1, 136.4, 132.1, 128.3, 126.8, 122.7, 120.8, 111.8, 80.7, 78.1, 75.8, 73.6, 70.2, 61.1, 55.7, 43.8; HRMS-ESI ($m/z$): [M+Na]$^+$ calculated for $C_{17}H_{22}O_7Na$ 361.1263, found 361.1262.

*4.1.4. (E)-4-(3-Hydroxy-4-methoxyphenyl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2e**)*

Obtained in 95% yield; white powder; mp: 198–199 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 9.22 (s, 1H), 7.47 (d, $J$=16.5 Hz, 1H), 7.14 (d, $J$=9.1 Hz, 1H) overlapping with 7.13 (s, 1H), 6.97 (d, $J$=9.1 Hz, 1H), 6.68 (d, $J$=16.2 Hz, 1H), 5.05 (d, $J$=5.4 Hz, 1H), 4.94 (d, $J$=4.5 Hz, 1H), 4.87 (d, $J$=4.8 Hz, 1H), 4.36 (t, $J$=5.4 Hz, 1H), 3.82 (s, 3H), 3.64–3.57 (m, 2H), 3.41–3.35 (m, 1H), 3.18–3.16 (m, 1H), 3.12–3.05 (m, 2H), 2.99–2.89 (m, 2H), 2.77 (dd, $J$=9.0, 16.2 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 197.8, 150.1, 146.7, 142.5, 127.3, 124.5, 121.6, 114.3, 112.0, 80.7, 78.2, 75.9, 73.6, 70.3, 61.1, 55.7, 43.2. Anal. Calcd for $C_{17}H_{22}O_8$: C 57.62, H 6.26; found: C 57.40, H 5.96.

*4.1.5. (E)-4-[4-(Benzyloxy)-3-methoxyphenyl]-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2f**)*

Obtained in 94% yield; white powder; mp: 134–135 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.53 (d, $J$=16.2 Hz, 1H), 7.47–7.36 (m, 6H), 7.25 (dd, $J$=1.8, 8.4 Hz, 1H), 7.09 (d, $J$=8.4 Hz, 1H), 6.87 (d, $J$=16.2 Hz, 1H), 5.14 (s, 2H), 5.06 (d, $J$=5.4 Hz, 1H), 4.95 (d, $J$=4.8 Hz, 1H), 4.87 (d, $J$=4.5 Hz, 1H), 4.36 (t, $J$=5.7 Hz, 1H), 3.83 (s, 3H), 3.64–3.57 (m, 2H), 3.41–3.36 (m, 1H), 3.18–3.16 (m, 1H), 3.08–3.07 (m, 2H), 2.98–2.90 (m, 2H), 2.78 (dd, $J$=8.7, 16.2 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 197.9, 149.9, 149.2, 142.4, 136.8, 128.5, 128.5, 128.0, 127.9, 127.6, 124.9, 123.0, 113.1, 110.7, 80.7, 78.2, 75.9, 73.6, 70.3, 69.8, 61.1, 55.7, 43.2. Anal. Calcd for $C_{24}H_{28}O_8$: C 64.85, H 6.35; found: C 64.60, H 6.24.

*4.1.6. (E)-4-p-Tolyl-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2g**)*

Obtained in 97% yield; white powder; mp: 158–160 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.62 (d, $J$=8.1 Hz, 2H) overlapping with 7.57 (d, $J$=15.9 Hz, 1H), 7.24 (d, $J$=7.8 Hz, 2H), 6.90 (d, $J$=16.5 Hz, 1H), 5.10 (d, $J$=5.4 Hz, 1H), 5.01 (br, 1H), 4.93 (br, 1H), 4.39 (t, $J$=5.7 Hz, 1H), 3.64–3.55 (m, 2H), 3.43–3.37 (m, 1H), 3.19–3.14 (m, 1H), 3.12–3.05 (m, 2H), 2.99–2.92 (m, 2H), 2.79 (dd, $J$=8.7, 16.2 Hz, 1H), 2.33 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 198.1, 142.1, 140.4, 131.8, 129.6, 129.6, 128.5, 128.5, 125.9, 80.7, 78.1, 75.8, 73.6, 70.2, 61.1, 43.3, 21.1; HRMS-ESI ($m/z$): [M+Na]$^+$ calculated for $C_{17}H_{22}O_6Na$ 345.1314, found 345.1309.

*4.1.7. (E)-4-(4-Fluorophenyl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2h**)*

Obtained in 91% yield; white powder; mp: 158–160 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.80 (m, 1H), 7.59 (d, $J$=16.5 Hz, 1H), 7.26 (t, $J$=9.0 Hz, 1H), 6.92 (d, $J$=16.5 Hz, 1H), 5.05 (d, $J$=5.5 Hz, 1H), 4.92 (d, $J$=4.5 Hz, 1H), 4.85 (d, $J$=5.0 Hz, 1H), 4.34 (t, $J$=5.7 Hz, 1H), 3.64–3.57 (m, 2H), 3.41–3.35 (m, 1H), 3.19–3.15 (m, 1H), 3.10–3.03 (m, 2H), 2.98–2.93 (m, 2H), 2.78 (dd, $J$=8.7, 16.5 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 198.0, 163.2 (d, $^1J_{C-F}$=248.0Hz), 140.8, 131.2, 130.7 (d, $^3J_{C-F}$=8.7 Hz), 130.7 (d, $^3J_{C-F}$=8.7 Hz), 126.7, 115.9 (d, $^2J_{C-F}$=21.0 Hz), 115.9 (d, $^2J_{C-F}$=21.0 Hz), 80.7, 78.1, 75.8, 73.6, 70.3, 61.1, 43.4; HRMS-ESI ($m/z$): [M+Na]$^+$ calculated for $C_{16}H_{19}FO_6Na$ 349.1063, found 349.1052.

*4.1.8. (E)-4-(3-Bromophenyl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2i**)*

Obtained in 97% yield; white powder; mp: 148–150 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.96 (s, 1H), 7.73 (d, $J$=7.8 Hz, 1H), 7.60 (d, $J$=7.8 Hz, 1H), 7.54 (d, $J$=16.2 Hz, 1H), 7.37 (t, $J$=7.5 Hz, 1H), 7.02 (d, $J$=16.2 Hz, 1H), 5.05 (d, $J$=6.0 Hz, 1H), 4.92 (d, $J$=4.8 Hz, 1H), 4.85 (d, $J$=4.5 Hz, 1H), 4.34 (t, $J$=5.7 Hz, 1H), 3.65–3.56 (m, 2H), 3.39–3.34 (m, 1H), 3.17–3.13 (m, 1H), 3.10–3.05 (m, 2H), 2.98–2.90 (m, 2H), 2.77 (dd, $J$=8.7, 16.5 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 198.0, 140.2, 137.1, 132.8, 131.0, 130.9, 128.1, 127.4, 122.3, 80.7, 78.1, 75.7, 73.6, 70.3, 61.1, 43.7. Anal. Calcd for $C_{16}H_{19}BrO_6$: C 49.63, H 4.95; found: C 49.90, H 5.13.

*4.1.9. (E)-4-[3-(Trifluoromethyl)phenyl]-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2j**)*

Obtained in 96% yield; white powder; mp: 142–145 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.11 (s, 1H), 8.05 (d, $J$=8.0 Hz, 1H), 7.77 (d, $J$=8.0 Hz, 1H), 7.68 (d, $J$=16.5 Hz, 1H) overlapping with 7.66 (m, 1H), 5.09 (d, $J$=5.5 Hz, 1H), 4.98 (br, 1H), 4.89 (br, 1H), 4.35 (t, $J$=5.5 Hz, 1H), 3.66–3.58 (m, 2H), 3.42–3.38 (m, 1H), 3.20–3.17 (m, 1H), 3.11–3.05 (m, 2H), 3.00–2.94 (m, 2H), 2.81 (dd, $J$=9.0, 16.5 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 198.1, 140.1, 135.8, 132.0, 130.0, 129.8 (q, $^2J_{C-F}$=31.1 Hz), 128.6, 126.5, 125.1, 124.0 (q, $^1J_{C-F}$=273.8 Hz), 80.7, 78.1, 75.7, 73.6, 70.3, 61.1, 43.7; HRMS-ESI ($m/z$): [M+Na]$^+$ calculated for $C_{17}H_{19}F_3O_6Na$ 399.1031, found 399.1029.

*4.1.10. (E)-4-(Furan-2-yl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2k**)*

Obtained in 90% yield; colorless oil; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.86 (d, $J$=2.0 Hz, 1H), 7.40 (d, $J$=16.0 Hz, 1H), 6.98 (d, $J$=3.5 Hz, 1H), 6.65 (dd, $J$=1.5, 3.5 Hz, 1H), 6.59 (d, $J$=16.0 Hz, 1H), 5.03 (d, $J$=6.0 Hz, 1H), 4.90 (m, 1H), 4.84 (d, $J$=5.0 Hz, 1H), 4.31 (t, $J$=5.7 Hz, 1H), 3.60–3.56 (m, 2H), 3.40–3.36 (m, 1H), 3.17–3.14 (m, 1H), 3.09–3.01 (m, 2H), 2.95–2.90 (m, 2H), 2.74 (dd, $J$=8.5, 16.0 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 197.5, 150.6, 145.9, 128.8, 123.6, 116.4, 112.9, 80.7, 78.1, 75.9, 73.5, 70.2, 61.1, 43.3; HRMS-ESI ($m/z$): [M+Na]$^+$ calculated for $C_{15}H_{20}O_6Na$ 321.0951, found 321.0943.

*4.1.11. (E)-4-(Thiophen-2-yl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2l**)*

Obtained in 92% yield; white powder; mp: 149–151 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.76 (d, $J$=16.5 Hz, 1H), 7.73 (d, $J$=5.0 Hz, 1H), 7.55 (d, $J$=3.5 Hz, 1H), 7.16 (dd, $J$=3.5, 5.0 Hz, 1H), 6.60 (d, $J$=16.5 Hz, 1H), 5.03 (d, $J$=6.0 Hz, 1H), 4.90 (d, $J$=4.5 Hz, 1H), 4.84 (d, $J$=5.0 Hz, 1H), 4.31 (t, $J$=6.0 Hz, 1H), 3.61–3.56 (m, 2H), 3.41–3.36 (m, 1H), 3.19–3.15 (m, 1H), 3.10–3.02 (m, 2H), 2.96–2.90 (m, 2H), 2.76 (dd, $J$=9.0, 16.5 Hz, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 197.5, 139.5,

134.9, 132.3, 129.9, 128.6, 125.3, 80.7, 78.1, 75.9, 73.6, 70.3, 61.1, 43.2. Anal. Calcd for $C_{14}H_{18}O_6S$: C 53.49, H 5.77; found: C 53.39, H 5.89.

*4.1.12. (E)-4-(Thiophen-2-yl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2m**)*

Obtained in 90% yield; white powder; mp: 174–176 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.76 (d, $J$=16.0 Hz, 1H), 7.73 (d, $J$=5.0 Hz, 1H), 7.56 (d, $J$=3.5 Hz, 1H), 7.16 (dd, $J$=4.0, 4.5 Hz, 1H), 6.59 (d, $J$=16.0 Hz, 1H), 4.67 (d, $J$=4.0 Hz, 1H), 4.63 (d, $J$=4.5 Hz, 1H), 4.42 (d, $J$=5.0 Hz, 1H), 4.28 (t, $J$=6.0 Hz, 1H), 3.82 (t, $J$=6.5 Hz, 1H), 3.65–3.57 (m, 2H), 3.42–3.37 (m, 1H), 3.32 (m, 2H), 3.03 (m, 1H), 2.94–2.84 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 197.3, 139.3, 134.9, 132.5, 129.9, 128.6, 125.2, 81.2, 74.7, 74.1, 70.3, 61.5, 42.0. Anal. Calcd for $C_{14}H_{18}O_6S\cdot0.5H_2O$: C 52.00, H 5.92; found: C 52.11, H 5.95.

*4.1.13. (E)-4-(Benzo[d][1,3]dioxol-5-yl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2n**)*

Obtained in 92% yield; white powder; mp: 170–171 °C; $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 7.51 (d, $J$=16.0 Hz, 1H), 7.40 (d, $J$=1.5 Hz, 1H), 7.21 (dd, $J$=1.5, 8.0 Hz, 1H), 6.97 (d, $J$=8.5 Hz, 1H), 6.80 (d, $J$=16.0 Hz, 1H), 6.08 (s, 2H), 4.67 (d, $J$=2.5 Hz, 1H), 4.63 (d, $J$=5.0 Hz, 1H), 4.42 (d, $J$=4.5 Hz, 1H), 4.29 (t, $J$=5.5 Hz, 1H), 3.84 (t, $J$=6.0 Hz, 1H), 3.65–3.63 (m, 1H), 3.58–3.57 (m, 1H), 3.41–3.37 (m, 1H), 3.37–3.28 (m, 2H), 3.04–3.01 (m, 1H), 2.94–2.84 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 197.8, 149.4, 148.1, 142.1, 128.9, 125.2, 124.9, 108.6, 106.7, 101.6, 81.2, 74.8, 74.1, 70.4, 67.2, 61.6, 42.1; ESI-TOF$^+$ ($m/z$): $[M+Na]^+$ calculated for $C_{22}H_{29}NO_8Na$ 375.1056, found 375.1733.

*4.1.14. (E)-4-(Benzo[d][1,3]dioxol-5-yl)-1-(3,4,5-trihydroxy-tetrahydro-2H-pyran-2-yl)but-3-en-2-one (**2o**)*

Obtained in 97% yield; white powder; mp: 96–98 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.51 (d, $J$=16.2 Hz, 1H), 7.40 (d, $J$=1.2 Hz, 1H), 7.21 (dd, $J$=1.5, 8.1 Hz, 1H), 6.97 (d, $J$=8.1 Hz, 1H), 6.79 (d, $J$=16.2 Hz, 1H), 6.09 (s, 2H), 5.10 (d, $J$=5.7 Hz, 1H), 4.99 (d, $J$=4.5 Hz, 1H), 4.94 (d, $J$=5.1 Hz, 1H), 3.64 (dd, $J$=5.1, 10.8 Hz, 1H), 3.57 (td, $J$=2.7, 9.5 Hz, 1H), 3.25 (td, $J$=5.1, 9.5 Hz, 1H), 3.11 (td, $J$=4.5, 8.6 Hz, 1H), 2.99–2.96 (m, 1H), 2.92 (t, $J$=4.2 Hz, 1H), 2.87 (d, $J$=2.7 Hz, 1H), 2.76 (dd, $J$=9.3, 15.9 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 198.2, 149.4, 148.1, 142.3, 128.9, 125.3, 125.1, 108.6, 106.7, 101.7, 78.2, 77.2, 73.6, 70.0, 69.8, 43.1. Anal. Calcd for $C_{16}H_{18}O_7\cdot0.5H_2O$: C 58.00, H 5.78; found: C 58.23, H 6.01.

*4.1.15. (E)-4-(3-Hydroxy-4-methoxyphenyl)-1-(3,4,5-trihydroxy-tetrahydro-2H-pyran-2-yl)but-3-en-2-one (**2p**)*

Obtained in 95% yield; white powder; mp: 198–200 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 9.22 (s, 1H), 7.45 (d, $J$=16.5 Hz, 1H), 7.13 (d, $J$=9.1 Hz, 1H) overlapping with 7.11 (s, 1H), 6.96 (d, $J$=9.1 Hz, 1H), 6.64 (d, $J$=16.2 Hz, 1H), 5.07 (d, $J$=6.0 Hz, 1H), 4.97 (d, $J$=4.5 Hz, 1H), 4.92 (d, $J$=4.8 Hz, 1H), 3.81 (s, 3H), 3.66–3.61 (m, 1H), 3.56–3.50 (m, 1H), 3.27–3.22 (m, 1H), 3.18–3.06 (m, 1H), 2.98–2.85 (m, 3H), 2.76 (dd, $J$=9.0, 15.6 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 198.1, 150.1, 146.7, 142.7, 127.2, 124.5, 121.6, 114.2, 111.9, 78.2, 77.3, 73.6, 69.9, 69.8, 55.6, 42.9. Anal. Calcd for $C_{16}H_{20}O_7$: C 59.25, H 6.22; found: C 59.00, H 6.33.

*4.1.16. (E)-4-(4-Hydroxy-3-methoxyphenyl)-1-(3,4,5-trihydroxy-tetrahydro-2H-pyran-2-yl)but-3-en-2-one (**2q**)*

Obtained in 95% yield; white powder; mp: 209–211 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 9.65 (s, 1H), 7.49 (d, $J$=16.2 Hz, 1H), 7.30 (d, $J$=1.8 Hz, 1H), 7.13 (dd, $J$=2.1, 8.7 Hz, 1H), 6.80 (d, $J$=8.1 Hz, 1H), 6.75 (d, $J$=15.9 Hz, 1H), 5.09 (d, $J$=5.7 Hz, 1H), 4.98 (d, $J$=4.5 Hz, 1H), 4.92 (d, $J$=5.1 Hz, 1H), 3.82 (s, 3H), 3.66–3.61 (m, 1H), 3.58–3.50 (m, 1H), 3.30–3.20 (m, 1H), 3.14–3.06 (m, 1H), 2.98–2.85 (m, 3H), 2.76 (dd, $J$=9.3, 15.6 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 198.0, 149.4, 147.9, 142.9, 125.9, 123.9, 123.3, 115.6, 111.3, 78.2, 77.2, 73.6, 69.9, 69.7, 55.7, 42.9. Anal. Calcd for $C_{16}H_{20}O_7\cdot0.6H_2O$: C 57.34, H 6.38; found: C 57.14, H 6.44.

*4.1.17. (E)-4-(4-Methoxyphenyl)-1-(3,4,5-trihydroxy-tetrahydro-2H-pyran-2-yl)but-3-en-2-one (**2r**)*

Obtained in 98% yield; white powder; mp: 120–122 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.68 (d, $J$=8.7 Hz, 2H), 7.55 (d, $J$=15.9 Hz, 1H), 7.00 (d, $J$=9.0 Hz, 2H), 6.77 (d, $J$=16.2 Hz, 1H), 5.09 (d, $J$=5.7 Hz, 1H), 4.98 (d, $J$=4.5 Hz, 1H), 4.93 (d, $J$=5.7 Hz, 1H), 3.80 (s, 3H), 3.64 (dd, $J$=5.1, 10.8 Hz, 1H), 3.55 (td, $J$=2.4, 9.3 Hz, 1H), 3.25 (td, $J$=5.1, 9.3 Hz, 1H), 3.11 (td, $J$=4.8, 10.2 Hz, 1H), 2.99–2.95 (m, 1H), 2.94–2.92 (m, 1H), 2.87 (d, $J$=2.4 Hz, 1H), 2.77 (dd, $J$=9.3, 15.9 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 198.2, 161.2, 142.2, 130.3, 130.3, 126.9, 124.7, 114.4, 114.4, 78.2, 77.2, 73.6, 69.9, 69.7, 55.3, 42.9. Anal. Calcd for $C_{16}H_{20}O_6\cdot0.25H_2O$: C 61.43, H 6.61; found: C 61.40, H 6.35.

*4.1.18. (E)-4-[4-(Dimethylamino)phenyl]-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]but-3-en-2-one (**2s**)*

Obtained in 60% yield; yellow powder; mp: 226–228 °C; $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.54 (d, $J$=9.0 Hz, 2H) overlapping with 7.49 (d, $J$=16.2 Hz, 1H), 6.72 (d, $J$=9.0 Hz, 2H) overlapping with 6.67 (d, $J$=16.2 Hz, 1H), 5.03 (d, $J$=5.4 Hz, 1H), 4.92 (br, 1H), 4.86 (d, $J$=3.6 Hz, 1H), 4.34 (t, $J$=5.7 Hz, 1H), 3.63–3.57 (m, 2H), 3.34 (m, 1H), 3.17–3.11 (m, 1H), 3.08–3.04 (m, 2H), 2.98 (s, 6H) overlapping with 2.98–2.85 (m, 2H), 2.73 (dd, $J$=8.7, 15.9 Hz, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 197.4, 151.8, 143.1, 130.2, 130.2, 121.6, 121.6, 111.8, 111.8, 80.7, 78.2, 76.0, 73.6, 70.3, 61.1, 43.0, 39.7, 39.7. Anal. Calcd for $C_{18}H_{25}NO_6\cdot0.3H_2O$: C 60.59, H 7.23, N 3.93; found: C 60.48, H 6.97, N 3.92.

*4.1.19. (E)-1-(Benzo[d][1,3]dioxol-5-yl)pent-1-en-3-one (**2u**)*

Obtained in 92% yield; white powder; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.47 (t, $J$=16.2 Hz, 1H), 7.06–7.01 (m, 2H), 6.82 (d, $J$=7.8 Hz, 1H), 6.58 (t, $J$=15.9 Hz, 1H), 6.01 (s, 2H), 2.67 (q, $J$=7.2 Hz, 2H), 1.16 (t, $J$=7.2 Hz, 3H).

*4.1.20. (E)-3-(Benzo[d][1,3]dioxol-5-yl)-1-(3-nitrophenyl)prop-2-en-1-one (**2v**)*

Obtained in 94% yield; yellow powder; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.82 (t, $J$=2.1 Hz, 1H), 8.45–8.44 (m, 1H), 8.42–8.41 (m, 1H), 8.36–8.35 (m, 1H), 8.33–8.32 (m, 1H), 7.82 (d, $J$=15.3 Hz, 1H), 7.71 (t, $J$=7.8 Hz, 1H), 7.37 (d, $J$=15.3 Hz, 1H), 7.20–7.15 (m, 2H), 6.87 (d, $J$=8.1 Hz, 1H), 6.06 (s, 2H).

*4.1.21. (E)-3-(Benzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (**2w**)*

Obtained in 80% yield; yellow powder; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.03 (d, $J$=9.0 Hz, 2H), 7.73 (d, $J$=15.6 Hz, 1H), 7.38 (d, $J$=15.6 Hz, 1H), 7.17–7.11 (m, 2H), 6.98 (d, $J$=9.0 Hz, 2H), 6.85 (d, $J$=7.8 Hz, 2H), 6.03 (s, 2H), 3.89 (s, 3H).

*4.1.22. (E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)cyclopentanone (**2xa**)*

Obtained in 85% yield; white powder; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.31 (t, $J$=2.7 Hz, 1H), 7.06 (d, $J$=9.3 Hz, 1H), 7.05 (s, 1H), 6.86 (d, $J$=7.8 Hz, 2H), 6.02 (s, 2H), 2.97–2.92 (m, 2H), 2.43–2.37 (m, 2H), 2.09–2.01 (m, 2H).

*4.1.23. (2E,5E)-2,5-Bis(benzo[d][1,3]dioxol-5-ylmethylene)-cyclopentanone (**2xb**)*

Obtained in 9% yield; yellow powder; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.70 (s, 2H), 7.02 (d, $J$=11.0 Hz, 2H), 6.99 (s, 2H), 6.84 (d, $J$=8.0 Hz, 2H), 6.00 (s, 4H), 3.07 (s, 4H).

*4.1.24. (E)-2-(Benzo[d][1,3]dioxol-5-ylmethylene)-cyclohexanone (**2ya**)*

Obtained in 36% yield; yellow powder; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 7.43 (t, $J$=2.0 Hz, 1H), 6.93 (d, $J$=8.0 Hz, 1H), 6.92 (s, 1H), 6.83 (d, $J$=8.0 Hz, 1H), 6.00 (s, 2H), 2.82 (ddd, $J$=2.0 Hz, 2H), 2.52 (t, $J$=7.0 Hz, 2H), 1.94–1.89 (m, 2H), 1.80–1.75 (m, 2H).

*4.1.25. (2E,6E)-2,6-Bis(benzo[d][1,3]dioxol-5-ylmethylene)-cyclohexanone (**2yb**)*

Obtained in 55% yield; yellow powder; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.70 (s, 2H), 7.00 (d, $J$=7.8 Hz, 2H), 6.98 (s, 2H), 6.85 (d, $J$=8.4 Hz, 2H), 6.00 (s, 4H), 2.90–2.87 (m, 4H), 1.82–1.78 (m, 2H).

*4.1.26. 4-Hydroxy-4-(4-nitrophenyl)-1-[3,4,5-trihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yl]butan-2-one (**3a**)*

Obtained in 73% yield; colorless oil; $^1$H NMR (300 MHz, $D_2O$): $\delta$ 8.05 (d, $J$=8.7 Hz, 1H), 7.42 (d, $J$=8.7 Hz, 1H), 5.17–5.13 (m, 1H), 3.62–3.52 (m, 2H), 3.48–3.43 (m, 1H), 3.31–3.21 (m, 1H), 3.19–3.15 (m, 2H), 3.05–2.85 (m, 3H), 2.80 (dd, $J$=3.0, 16.5 Hz, 1H), 2.60–2.49 (m, 1H); $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ 213.2, 153.0, 149.7, 129.6, 129.5, 126.5, 126.5, 82.1, 79.8, 77.8, 75.6, 72.3, 71.1, 63.3, 53.3, 47.9. HRMS-ESI ($m/z$): $[M+Na]^+$ calculated for $C_{16}H_{21}NO_9Na$ 394.1114, found 394.1115.

## 4.2. Capture of the key intermediate VI

A mixture of compound **1a** (0.5 mmol), an aldehyde (0.6 mmol), and proline–TEA (0.55 mmol) in 1.0 mL of anhydrous $CH_3OH$ was stirred at room temperature for 30–80 min. The endpoint of the reaction was monitored by TLC. The resulting mixture was purified by preparative TLC.

*4.2.1. Compound **VIc***

Yellow powder. $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ 7.99 (d, $J$=15.5 Hz, 1H), 7.75 (d, $J$=9.0 Hz, 2H), 7.03 (d, $J$=8.5 Hz, 2H) overlapping with 6.99 (d, $J$=16.0 Hz, 1H), 4.98 (dd, $J$=4.0, 8.5 Hz, 1H), 4.39–4.31 (m, 1H), 4.26–4.21 (m, 1H), 3.87 (s, 3H), 3.83–3.81 (m, 1H), 3.78–3.74 (m, 1H), 3.72–3.68 (m, 1H), 3.65–3.54 (m, 2H), 3.36–3.15 (m, 4H), 2.50–2.42 (m, 1H), 2.40–2.33 (m, 1H), 2.20–1.96 (m, 2H). ESI-TOF$^+$ ($m/z$): $[(M+H)^+]$ calculated for $C_{22}H_{30}NO_8$ 436.1971; found 436.2695; $[(M+Na)^+]$ calculated for $C_{22}H_{29}NO_8Na$ 458.1791; found 458.2539.

*4.2.2. Compound **VIs***

Obtained in 90% yield; red powder; $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 7.92 (d, $J$=15.3 Hz, 1H), 7.63 (d, $J$=9.0 Hz, 2H), 6.78 (d, $J$=9.3 Hz, 2H) overlapping with 6.77 (d, $J$=13.8 Hz, 1H), 4.61 (br, 1H), 4.35–4.28 (m, 1H), 4.17–4.13 (m, 1H), 3.77 (dd, $J$=2.4, 11.7 Hz, 1H), 3.68–3.51 (m, 3H), 3.31–3.10 (m, 5H), 3.10 (s, 6H), 2.48–2.39 (m, 1H), 2.34–2.28 (m, 1H), 2.14–2.06 (m, 2H); $^{13}$C NMR (75 MHz, $CD_3OD$): $\delta$ 175.2, 174.2, 155.5, 154.9, 133.8, 133.8, 123.1, 113.1, 113.1, 112.9, 81.7, 81.2, 79.4, 75.5, 71.4, 69.6, 62.8, 55.8, 40.2, 40.2, 35.1, 31.8, 24.4. ESI-TOF$^+$ ($m/z$): $[(M+H)^+]$ calculated for $C_{23}H_{33}N_2O_7$ 449.2288; found 449.3670; $[(M+Na)^+]$ calculated for $C_{23}H_{32}N_2O_7Na$ 471.2107; found 471.3553.

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## Supplementary data

$^1$H NMR, $^{13}$C NMR, HRMS and elemental analysis spectra for all the products are provided as supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.052.

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