

## COMMUNICATION

View Article Online  
View Journal | View IssueCite this: *Org. Biomol. Chem.*, 2024, **22**, 496Received 16th November 2023,  
Accepted 20th December 2023

DOI: 10.1039/d3ob01862h

rsc.li/obc

# Bi(OTf)<sub>3</sub>-promoted cascade annulation of hydroxy-pyranones and unsaturated $\gamma$ -ketoesters for the construction of polycyclic bridged pyrano-fuopyranones†

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An efficient protocol for constructing complex three dimensional polycyclic bridged chromano-fuopyranones and pyrano-fuopyranones (closely related to bioactive natural products) *via* bismuth (iii)-catalyzed cascade annulation of hydroxy-pyranones and unsaturated  $\gamma$ -ketoesters is presented. This process involves intermolecular Michael addition, intramolecular hemiketalization, lactonization, formation of one C–C bond and two C–O bonds, rings, and contiguous stereocenters.

Chromane and pyrone-fused fuo-pyranones are found in natural products and pharmaceuticals, with various applications, including cellular imaging and solar cells.<sup>1</sup> For instance, (+)-penicipyrene, isolated from the fungus *Penicillium sp.* PSU-F44, exhibits antibacterial activity.<sup>2</sup> On the other hand, (–)-tenuipyrene was isolated from the entomopathogenic fungus *Isaria tenuipes* in the presence of epigenetic modifying agents, including a histone deacetylase inhibitor and a DNA methyltransferase inhibitor.<sup>3</sup> Pyripyropenes A–D, isolated from *Aspergillus fumigatus* FO-1289, are potent acyl-CoA inhibitors and stand out as the most potent naturally derived ACAT inhibitors, with nanomolar IC<sub>50</sub> values in rat liver microsomes.<sup>4</sup> Arisugacin functions as an acetylcholinesterase (AChE) inhibitor, while territrem A–C, with a pyranopyran skeleton, selectively inhibit human AChE (Fig. 1).<sup>5,6</sup> The intriguing aspects of these features have led to a sustained emphasis on developing efficient methodologies for synthesizing chroman/pyrone-derived scaffolds in synthetic chemistry.<sup>7</sup>

In this context, Tong and co-workers disclosed an expedited strategy for constructing pyrone-tethered [5,6]-spiroketals through amberlyst-15 promoted intermolecular annulative cyclo-ketalization (proceeds through Michael addition/hemiketalization and spiroketalization sequence) of 4-hydroxy 6-methyl-2-pyrone with  $\alpha,\beta$ -unsaturated 1,3-diketones. This

strategy was successfully employed in their biomimetic total synthesis of (–)-penicipyrene and (–)-tenuipyrene (entry 1a, Scheme 1).<sup>8</sup> In 2020, Zhang's group reported an organocatalytic asymmetric reaction involving 4-hydroxycoumarins and 2-hydroxy cinnamaldehydes. This reaction proceeded *via* conjugate addition, facilitating the construction of chiral bridged acetals (Scheme 1).<sup>9</sup>

In continuation of our interest in developing atom and step-efficient cascade annulation reactions utilizing Lewis acid catalysis,<sup>10</sup> recently, we unveiled a Fe(III)-catalyzed cascade annulation involving electron-rich hydroxyarenes and suitably functionalized unsaturated  $\gamma$ -ketoesters.<sup>11</sup> This approach enabled the synthesis of polycyclic bridged/fused 2-chromanol lactones, introducing three new bonds, stereocenters, and new rings into the molecular framework (entry 1b, Scheme 1).<sup>12</sup> Herein, we report the unprecedented synthesis of polycyclic bridged chromano (pyrano)-fuopyranones 3/5 (which represent lactone analogs akin to penicipyrene and tenuipyrene) through bismuth(III)-catalyzed<sup>10,12</sup> cascade annulation of chromenones/hydroxy-pyranones 1/4 and unsaturated  $\gamma$ -ketoesters 2 (entry 2, Scheme 1).

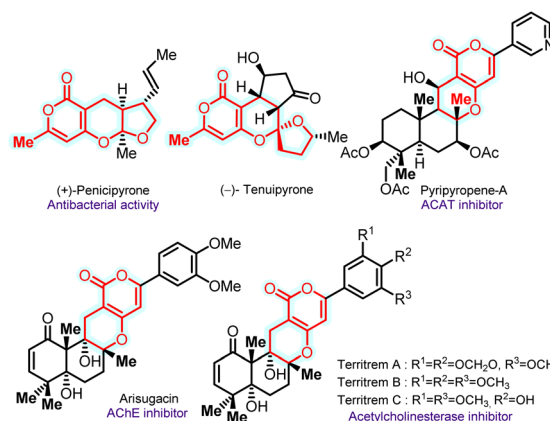


Fig. 1 Natural products containing fused pyrano-fuopyran moiety.

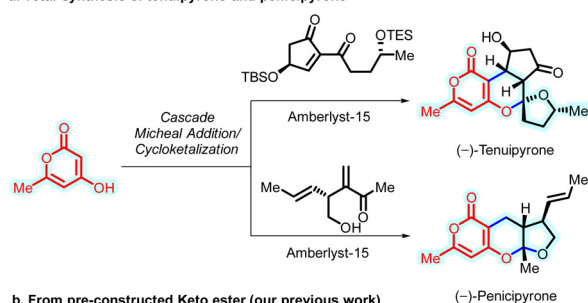
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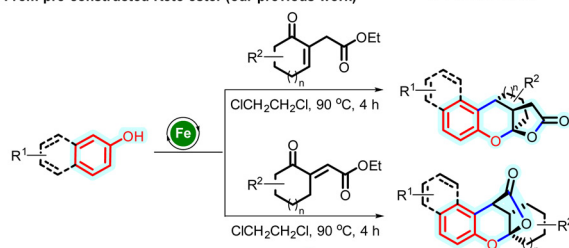
† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3ob01862h>

## 1. Previous work

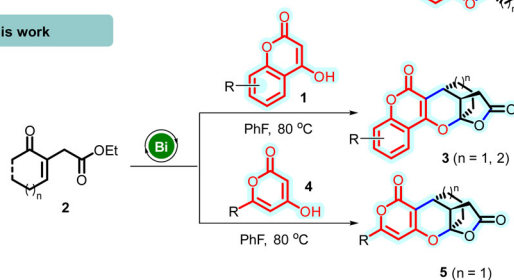
## a. Total synthesis of tenuipyron and penicipyron



## b. From pre-constructed Keto ester (our previous work)



## 2. This work



**Scheme 1** Previous cascade annulation approaches to access furo-pyr-anones, and our present work.

We initiated the reaction optimization studies by selecting commercially available 4-hydroxycoumarin (**1a**) and known<sup>12</sup> unsaturated  $\gamma$ -ketoester **2a** (featuring cyclohexenone Michael acceptor) as substrates (Table 1). Drawing from our previous research and guided by literature examples involving Brønsted acid catalysis in Michael addition-induced cascade processes, we began by assessing various catalysts such as TfOH, TFA, *p*-TSA, PPTS, and Amberlyst-15 (used at 20 mol%) in combination with DCE as the reaction medium. These initial reactions did not progress at room temperature (27 °C). Encouragingly, we found that TfOH, TFA, and amberlyst-15 demonstrated varying degrees of activity, leading to the formation of the desired annulation product **3aa** with isolated yields of 41%, 24%, and 17% for product **3aa**, respectively at 80 °C (entries 1–5 in Table 1). The product **3aa** was confirmed through <sup>1</sup>H and <sup>13</sup>C NMR (DEPT) and HRMS analyses and further verified by comparing the obtained data to our previously reported findings for similar bridged ketal-lactones (Table 1).<sup>12</sup>

Subsequently, our focus shifted towards investigating the impact of various Lewis acids on this annulation process.<sup>14,15</sup> To this end, we initially employed the conditions we had previously identified<sup>12</sup> 20 mol% of Fe(OTf)<sub>3</sub> in DCE at 80 °C. Under these conditions, **3aa** was obtained in an improved yield

**Table 1** Optimization studies<sup>a</sup>

| Entry | Catalyst                           | Solvent | Yield <sup>b</sup> (%) |
|-------|------------------------------------|---------|------------------------|
| 1     | TfOH                               | DCE     | 41                     |
| 2     | TFA                                | DCE     | 24                     |
| 3     | PTSA                               | DCE     | – <sup>c</sup>         |
| 4     | PPTS                               | DCE     | – <sup>c</sup>         |
| 5     | Amberlyst-15                       | DCE     | 17                     |
| 6     | Fe(OTf) <sub>3</sub>               | DCE     | 51                     |
| 7     | AgOTf                              | DCE     | 24                     |
| 8     | Cu(OTf) <sub>2</sub>               | DCE     | 37                     |
| 9     | Sc(OTf) <sub>3</sub>               | DCE     | 20                     |
| 10    | BF <sub>3</sub> ·Et <sub>2</sub> O | DCE     | 18                     |
| 11    | Bi(OTf) <sub>3</sub>               | DCE     | 70                     |
| 12    | Bi(OTf) <sub>3</sub>               | PhF     | 76                     |
| 13    | No catalyst                        | PhF     | – <sup>c</sup>         |

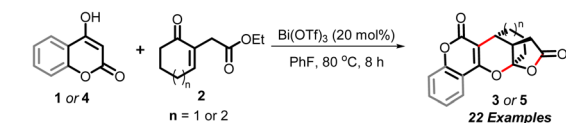
<sup>a</sup> Unless otherwise specified the reaction was performed with **1a** (0.55 mmol), **2a** (0.55 mmol), catalyst (20 mol%), and in indicated solvent (anhydrous, 2 mL) at 80 °C. <sup>b</sup> Isolated yield of **3aa**. <sup>c</sup> No conversion was observed.

of 51% in an 8-hour reaction (entry 6, Table 1). Expanding our exploration, we subjected the reaction to different metal triflates catalysts including AgOTf, Cu(OTf)<sub>2</sub>, Sc(OTf)<sub>3</sub>, and BF<sub>3</sub>·Et<sub>2</sub>O. However, these alternative Lewis acids resulted in comparably lower yields of **3aa** when compared to Fe(OTf)<sub>3</sub> (entries 7–10). The reaction using 20 mol% of Bi(OTf)<sub>3</sub> in DCE at 80 °C resulted in an improved yield of 70% (entry 11). Interestingly, when employing PhF as the solvent, the reaction furnished **3aa** with a favorable outcome of 76% and exhibited a clean thin-layer chromatography (TLC) profile (entry 12).

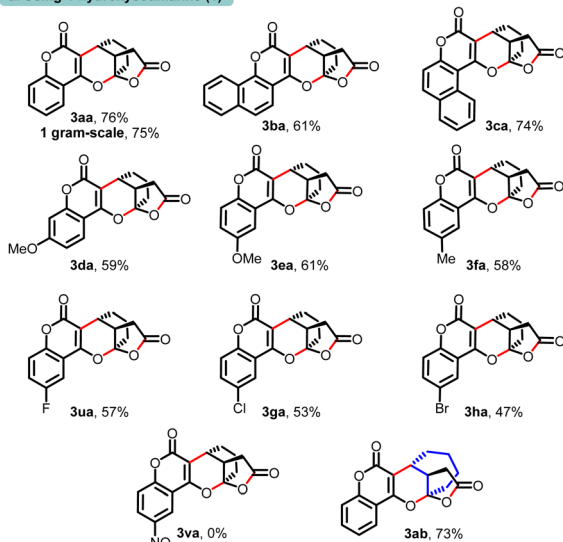
As anticipated, the reaction failed to progress in the absence of the catalyst, leading to full recovery of both annulation partners **1a** and **2a** (entry 13) (Table 1). Notably, Bi(OTf)<sub>3</sub> displayed moderate activity when PhCl, THF, and CH<sub>3</sub>CN were used as solvents (entries 1–3, Table S1†), while its activity ceased when solvents like DMF, toluene, MeOH, and EtOH were employed (entries 4–7, Table S1†).<sup>13</sup> Further alteration of reaction parameters like molar ratios of substrates and catalyst (Bi(OTf)<sub>3</sub> loading (5 and 10 mol%, entries 8 and 9, Table S1†) did not lead to discernible improvement.<sup>13</sup> Ultimately, it was determined that the ideal conditions for this cascade annulation reaction were the use of Bi(OTf)<sub>3</sub> (20 mol%) in PhF at 80 °C (entry 12, Table 1).

With the optimal reaction condition in hand, we next evaluated the scope and generality of this cascade reaction concerning the 4-hydroxy pyranones (**1**) and unsaturated  $\gamma$ -ketoesters **2** possessing diverse substituents (Scheme 2).

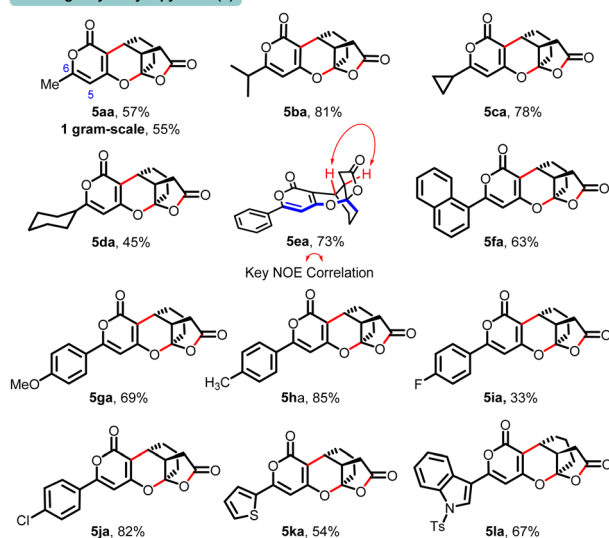
The reaction involving 4-hydroxy-2H-chromen-2-ones possessing phenyl,  $\alpha$ -naphthyl, and  $\beta$ -naphthyl segments (**1a–1c**) proceeded well with cyclohexenone-tethered ketoester **2a**, and delivered corresponding polycyclic adducts **3aa–3ca** in good yields ranging from 61% to 76%. Moving forward, hydroxy-chromenones containing electron-donating substituents



## a. Using 4-hydroxycoumarins (1)

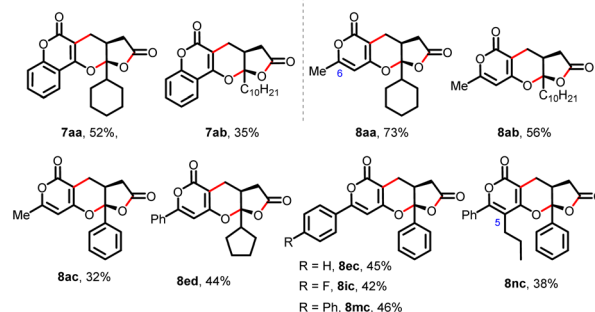
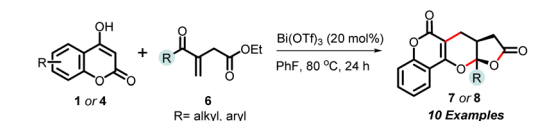


## b. Using 4-hydroxy-2-pyrones (4)



**Scheme 2** Scope of the cascade annulation of hydroxy-chromenones/hydroxy-pyranones (1/4) with cycloalkenone-tethered unsaturated  $\gamma$ -ketoesters (2).

(–OMe, –Me) **1d**, **1e** and **1f** were treated with **2a**, which furnished products **3da**, **3ea**, and **3fa**. Halogenated substrates **1** also reacted well and delivered adducts **3ua**, **3ga**, and **3ha** in good yields. Conversely, hydroxy-chromenones having electron-withdrawing substituents (–NO<sub>2</sub>) did not engage in the reaction with **2a**, and both starting materials were recovered. Interestingly, cycloheptenone bearing ketoester **2b** also participated well in the annulation with hydroxy-2H-chromen-2-one (**1a**), culminating in the formation of product **3ab** with a yield of 73% (entry a, Scheme 3). Whereas cyclopentenone-bearing ketoester **2c** failed to participate in the annulation.<sup>13</sup>

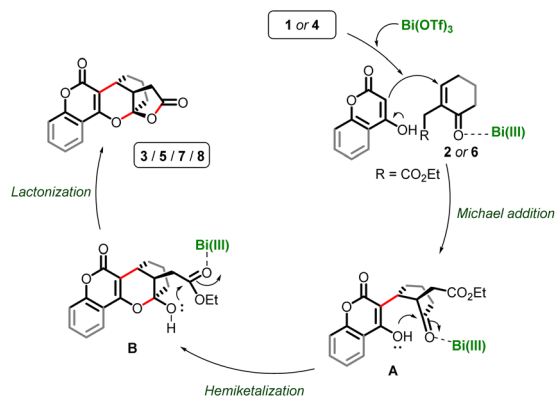


**Scheme 3** Scope of the cascade annulation of hydroxy-chromenones/hydroxy-pyranones (1/4) with acyclic enone-tethered unsaturated  $\gamma$ -ketoesters (6).

Expanding on our protocol, we explored the reactions of 6-substituted hydroxy-pyranones **4** using optimized conditions. Encouragingly, diverse substituents at C-6 (–methyl, –i-Pr, –cyclopropyl, cyclohexyl, phenyl,  $\alpha$ -naphthyl, anisyl, tolyl, *p*-fluoro-phenyl, *p*-chloro-phenyl) successfully reacted with cyclohexenone-tethered ketoester **2a**, yielding (pyrano)-furofuranones adducts **5aa–5ja** in yields ranging from 45% to 85%. Additionally, pyranones derived from heteroarenes (thiophenyl and *N*-tosyl-indolyl) produced **5ka** and **5la** in yields of 54% and 67%, respectively. Notably, C-5 substituted pyranones did not engage in this annulation (entry b, Scheme 2).<sup>13</sup> Next, we demonstrated the practicality and scalability of this protocol by conducting reactions on a 1.0-gram scale of **1a** and **4a**, resulting in good yields of **3aa** and **5aa**. The relative stereochemistry of these adducts was assigned based on our previous report,<sup>11</sup> NOE correlations of **5ea**, and analogy.<sup>13</sup>

Encouraged by these results, we investigated the reactivity of unsaturated  $\gamma$ -ketoesters **6**, which contain an acyclic enone and diverse substituents (cyclohexyl, decyl, phenyl, cyclopentyl), with hydroxy chromenone (**1a**) and various pyranones (**4**). All these reactions proceeded well, delivering the corresponding chromenone-derived adducts (**7aa** and **7ab**), as well as pyrone-tethered adducts (**8aa–8ac**, **8ed**, **8ec**, **8ic** and **8mc**), in moderate yields in 24 hours. Interestingly, the C-5 substituted pyrone (**4n**) also participated in this annulation, yielding **8nc** in a 38% yield (Scheme 3).

Based on previous reports from our group<sup>11</sup> and others,<sup>8,9</sup> as well as the results obtained in this study, we propose a plausible mechanistic sequence for this cascade annulation, outlined in Scheme 4.<sup>8,10–12</sup> The Bi(III)-activated enone partners **2/6**, trigger the Michael addition with the electron-rich hydroxy-chromen(pyran)-one **1/4**, resulting in the formation of intermediate **A**. Subsequent intramolecular hemiketalization of **A** leads to the formation of intermediate **B**. This hemiketal intermediate **B** then undergoes Bi(III)-facilitated lactonization, yielding chromano(pyran)-furofuranones **3/5/7/8**.



**Scheme 4** Plausible reaction mechanism.

In conclusion, we have developed a novel protocol for synthesizing intricate polycyclic bridged chromano-fuopyranones and pyrano-fuopyranones, which are relevant to bio-active natural compounds. This approach involves the Bi(III)-catalyzed cascade annulation of hydroxy-chromenones/hydroxy-pyranones with unsaturated  $\gamma$ -ketoesters. The reaction pathway encompasses a sequence of transformations, including Michael addition, hemiketalization, and lactonization. Our method has successfully yielded diverse three-dimensional polycyclic adducts akin to natural products such as tenuipyrone and penicipyron, achieving favorable yields. Notably, the practicality of this methodology has been demonstrated through gram-scale experiments. Ongoing efforts are directed toward exploring the biological activities of these synthesized products, and we anticipate publishing these findings in due course.

## Author contributions

R. K. conceived the project and directed the research work. A. B. R, B. R. B, and P. I. S conducted synthetic experiments, analyzed data, and prepared ESI. All authors commented on the manuscript and the ESI.†

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We express our sincere gratitude for the funding received from the SERB (Science & Engineering Research Board), New Delhi, India (Grant No. CRG/2020/001875). Additionally, B. R. B. would like to thank UGC-India, and P. I. S. extends appreciation to DST-Inspire for granting the Senior Research Fellowships (SRF).

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