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$Bi(OTf)_3$-promoted cascade annulation of hydroxy-pyranones and unsaturated γ-ketoesters for the construction of polycyclic bridged pyrano-furopyranones†

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An efficient protocol for constructing complex three dimensional polycyclic bridged chromano-furopyranones and pyrano-furopyranones (closely related to bioactive natural products) *via* bismuth(III)-catalyzed cascade annulation of hydroxy-pyranones and unsaturated γ-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 furo-pyranones are found in natural products and pharmaceuticals, with various applications, including cellular imaging and solar cells.[1] For instance, (+)-penicipyrone, isolated from the fungus *Penicillium sp*. PSU-F44, exhibits antibacterial activity.[2] On the other hand, (−)-tenuipyrone 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.[3] 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_{50} values in rat liver microsomes.[4] Arisugacin functions as an acetylcholinesterase (AChE) inhibitor, while territrems A–C, with a pyranopyran skeleton, selectively inhibit human AChE (Fig. 1).[5,6] 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.[7]

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/hemiketolization and spiroketalization sequence) of 4-hydroxy 6-methyl-2-pyrone with α,β-unsaturated 1,3-diketones. This strategy was successfully employed in their biomimetic total synthesis of (−)-penicipyrone and (−)-tenuipyrone (entry 1a, Scheme 1).[8] 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).[9]

In continuation of our interest in developing atom and step-efficient cascade annulation reactions utilizing Lewis acid catalysis,[10] recently, we unveiled a Fe(III)-catalyzed cascade annulation involving electron-rich hydroxyarenes and suitably functionalized unsaturated γ-ketoesters.[11] 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).[12] Herein, we report the unprecedented synthesis of polycyclic bridged chromano (pyrano)-furopyranones **3**/**5** (which represent lactone analogs akin to penicipyrone and tenuipyrone) through bismuth(III)-catalyzed[10,12] cascade annulation of chromenones/hydroxy-pyranones **1**/**4** and unsaturated γ-ketoesters **2** (entry 2, Scheme 1).

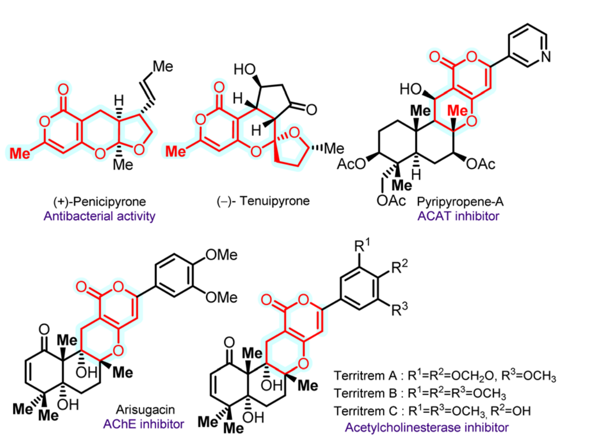

Fig. 1 Natural products containing fused pyrano-furopyran moiety.

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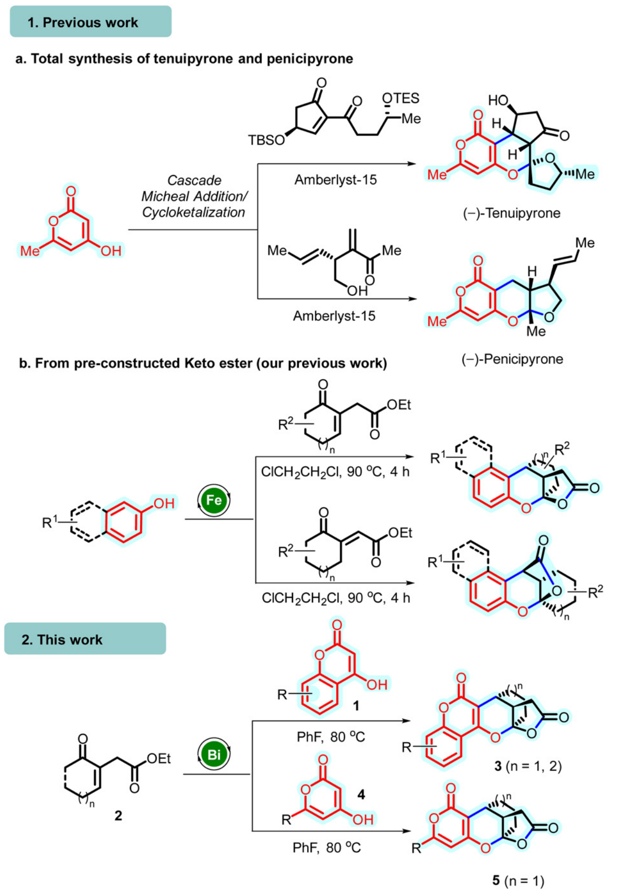
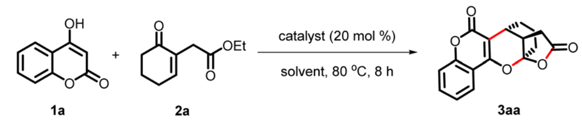


Scheme 1 Previous cascade annulation approaches to access furo-pyranones, and our present work.

We initiated the reaction optimization studies by selecting commercially available 4-hydroxycoumarin (**1a**) and known[12] unsaturated γ-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 ^{1}H and ^{13}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).[12]

Subsequently, our focus shifted towards investigating the impact of various Lewis acids on this annulation process.[14,15] To this end, we initially employed the conditions we had previously identified[12] 20 mol% of $Fe(OTf)_3$ in DCE at 80 °C. Under these conditions, **3aa** was obtained in an improved yield

Table 1 Optimization studies[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	TfOH	DCE	41
2	TFA	DCE	24
3	PTSA	DCE	–[c]
4	PPTS	DCE	–[c]
5	Amberlyst-15	DCE	17
6	$Fe(OTf)_3$	DCE	51
7	AgOTf	DCE	24
8	$Cu(OTf)_2$	DCE	37
9	$Sc(OTf)_3$	DCE	20
10	$BF_3 \cdot Et_2O$	DCE	18
11	$Bi(OTf)_3$	DCE	70
12	**$Bi(OTf)_3$**	**PhF**	**76**
13	No catalyst	PhF	–[c]

[a] 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. [b] Isolated yield of **3aa**. [c] 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, $Cu(OTf)_2$, $Sc(OTf)_3$, and $BF_3 \cdot Et_2O$. However, these alternative Lewis acids resulted in comparably lower yields of **3aa** when compared to $Fe(OTf)_3$ (entries 7–10). The reaction using 20 mol% of $Bi(OTf)_3$ 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, $Bi(OTf)_3$ displayed moderate activity when PhCl, THF, and CH_3CN 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†).[13] Further alteration of reaction parameters like molar ratios of substrates and catalyst ($Bi(OTf)_3$) loading (5 and 10 mol%, entries 8 and 9, Table S1†) did not lead to discernible improvement.[13] Ultimately, it was determined that the ideal conditions for this cascade annulation reaction were the use of $Bi(OTf)_3$ (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 γ-ketoesters **2** possessing diverse substituents (Scheme 2).

The reaction involving 4-hydroxy-2*H*-chromen-2-ones possessing phenyl, α-naphthyl, and β-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, hydroxychromenones containing electron-donating substituents

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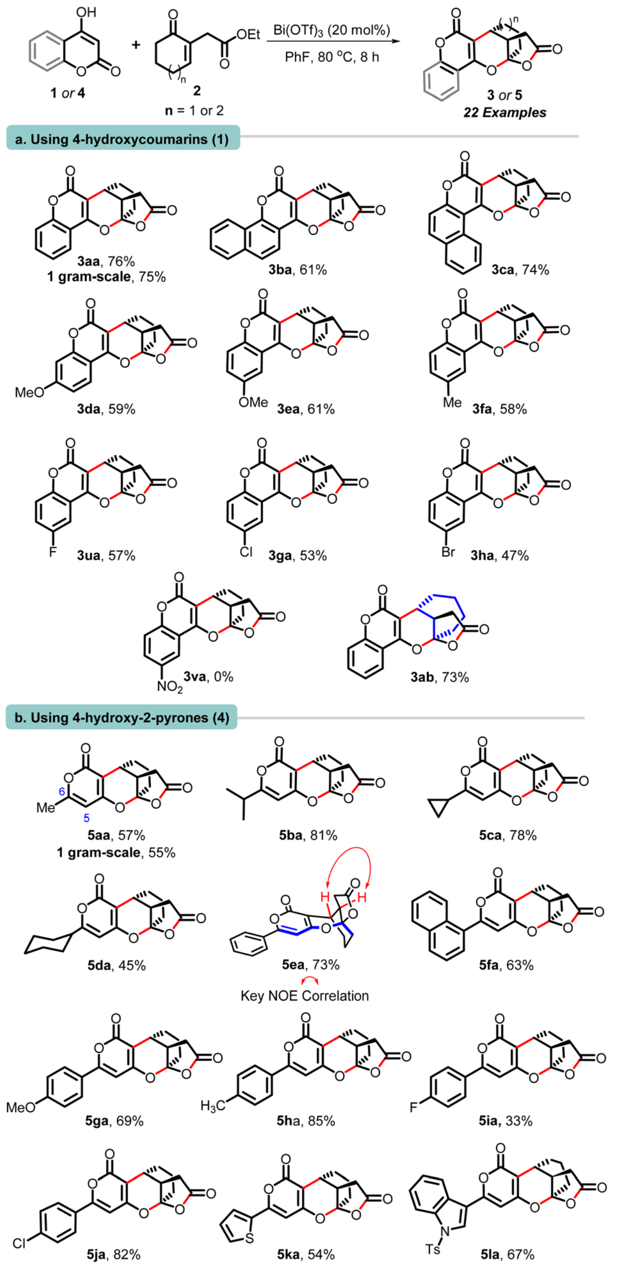
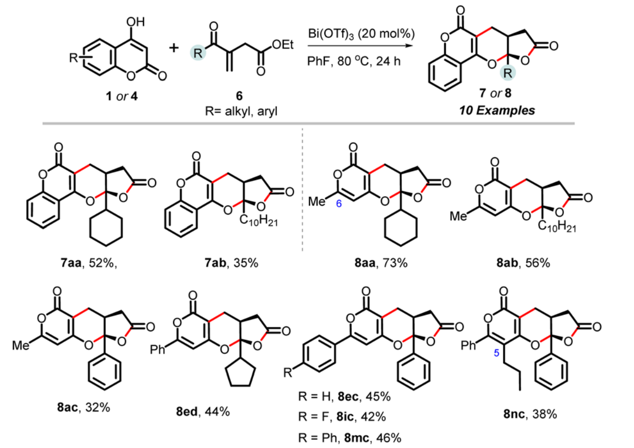


Scheme 2 Scope of the cascade annulation of hydroxy-chromenones/hydroxy-pyranones (**1/4**) with cycloalkenone-tethered unsaturated γ-ketoesters (**2**).



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

(–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_2) 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-2*H*-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.[13]

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, α-naphthyl, anisyl, tolyl, *p*-fluoro-phenyl, *p*-chloro-phenyl) successfully reacted with cyclohexenone-tethered ketoester **2a**, yielding (pyrano)-furopyranones 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 pyrones did not engage in this annulation (entry b, Scheme 2).[13] 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,[11] NOE correlations of **5ea**, and analogy.[13]

Encouraged by these results, we investigated the reactivity of unsaturated γ-ketoesters **6**, which contain an acyclic enone and diverse substituents (cyclohexyl, decyl, phenyl, cyclopentyl), with hydroxy chromenone (**1a**) and various pyrones (**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[11] and others,[8,9] as well as the results obtained in this study, we propose a plausible mechanistic sequence for this cascade annulation, outlined in Scheme 4.[8,10–12] 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(pyrano)-furopyranones **3/5/7/8**.

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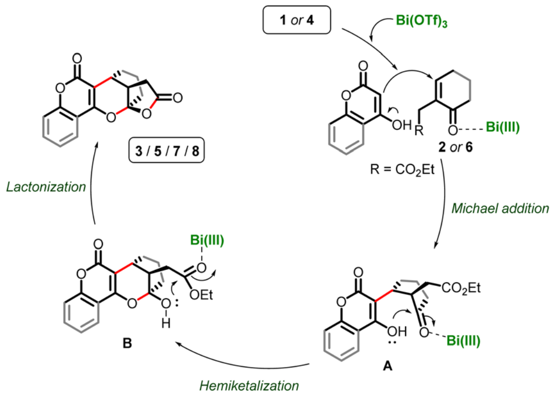

Scheme 4 Plausible reaction mechanism.

In conclusion, we have developed a novel protocol for synthesizing intricate polycyclic bridged chromano-furopyranones and pyrano-furopyranones, which are relevant to bioactive natural compounds. This approach involves the Bi(III)-catalyzed cascade annulation of hydroxy-chromenones/hydroxy-pyranones with unsaturated γ-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 penicipyrone, 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.

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