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Fe(III)-Catalyzed Diastereoselective Friedel−Crafts Alkylation−Hemiketalization−Lactonization Cascade for the Synthesis of Polycyclic Bridged 2-Chromanol Lactones

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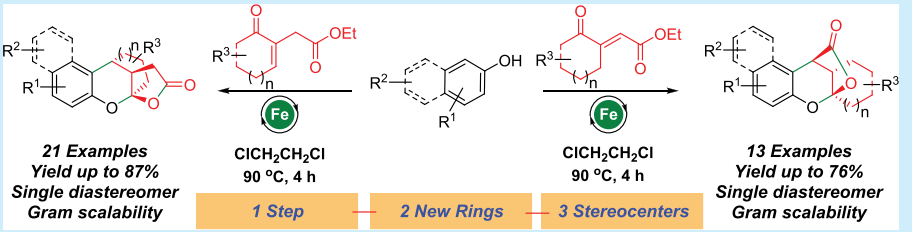
Supporting Information



ABSTRACT: An unprecedented Fe(III)-catalyzed Friedel−Crafts alkylation−hemiketalization−lactonization cascade of electron-rich hydroxy arenes and distinctively functionalized unsaturated 4-keto esters is developed for the construction of polycyclic bridged 2-chromanol lactones. Following this simple and facile protocol, a broad range of products was prepared in good to excellent yields as a single diastereomer. An unusual conglomerate (enantiomerically pure polymorph) of **3ac** is reported along with the absolute stereochemistry, and the remaining products were rigorously confirmed by single-crystal X-ray analysis and analogy.

The structural complexity of natural products combined with their biological relevance is a long-standing inspiration for the development of novel synthetic methodologies. In recent times, the development of cascade/domino reactions that provide complex three-dimensional architectures from readily accessible and structurally simple building blocks is emerging as one of the advanced fields of organic synthesis.[1] The chromane-derived scaffolds with bicyclic and tricyclic ketal skeletons are frequently encountered in many natural products that possess a broad range of biological activities. For instance, myrtucommuacetalone[2] (antiproliferative, IC_{50} = < 0.5 μg/mL), myrtucommulone J[3] (antibacterial, MIC = 0.38 μM), bullataketals[4] A and B (cytotoxic against P388 cell line, IC_{50} = 1.0 μg/mL), dracoflavan B[5] (alfa-amylase inhibitor, IC_{50} = 27 μM), enokipodins[6] A and C (antimicrobial), and chaetophenol[7] C (anticancer, HDAC inhibitor) are prominent examples and inspired several research groups to develop efficient methodologies to construct these scaffolds (Figure 1). In this context, Qiu and Tan's expeditious TFA/PTSA-mediated cascade reaction of hydroxy arenes and keto-alcohols,[8] Chen and Qiu's TFA-catalyzed [3 + 3]-type cycloaddition reaction to access the tricyclic core of bullataketals,[9] Wang and Bu's construction of bridged ketal spirooxindoles through a TfOH-promoted Michael addition based cascade,[10] Bencivenni et al.'s report of an enantioselective cascade of naphthols with α,β-unsaturated ketones using iminium catalysis,[11a] and Venkateswaran's intramolecular ketene olefin cycloaddition followed by an oxidative ring enlargement to generate the tricyclic chromanol lactone[11b] are notable examples. To the best of our knowledge, there is no report on the synthesis of related bridged 2-chromanol lactones utilizing a tandem process.

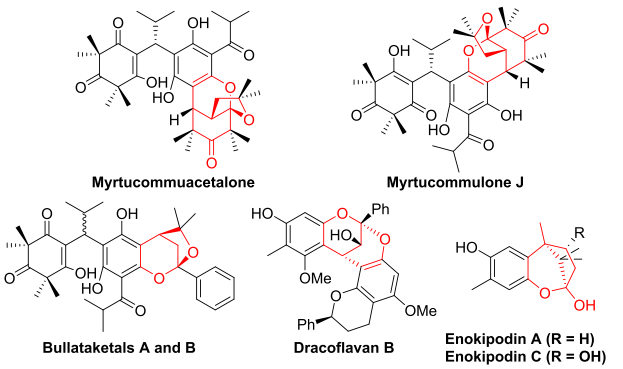


Figure 1. Selected biologically active natural products containing a chroman−ketal ring system.

In continuation of our interest in the development of cascade processes for the construction of scaffolds related to natural products[12] and inspired by the interesting biological profile of natural products possessing chroman ketal and

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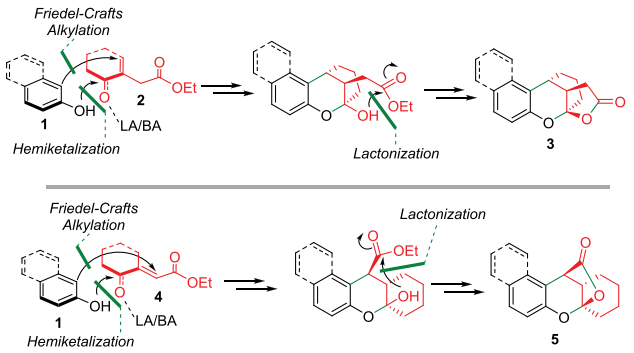
lactone[13] motifs, herein we report an unprecedented cascade process comprising a Fe(III)-catalyzed Friedel–Crafts alkylation–hemiketalization–lactonization sequence to access polycyclic bridged 2-chromanol-lactones from electron-rich hydroxy arenes and distinctively functionalized unsaturated 4-keto esters, which proceeds in a single step to deliver bridged tricycle through the formation of three new chemical bonds and three stereocenters.

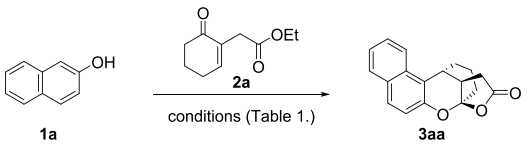
We hypothesized that it might be possible to develop a catalytic process for the synthesis of two differently bridged 2-chromanol lactones **3** (bearing 3a,4-dihydro-4,9a-propanofuro-[2,3-*b*]chromen-2(3*H*)-one skeleton) and **5** (possessing the 1,2,3,4,9,9a-hexahydro-4a,9-(epoxymethano)xanthen-11-one skeleton) through an intermolecular Friedel–Crafts alkylation of electron-rich hydroxy arene **1** with suitably functionalized keto esters possessing ethyl 3-methylene-4-oxopentanoate **2** or ethyl (*E*)-4-oxopent-2-enoate **4** motifs followed by intramolecular diastereoselective hemiketaliztion and subsequent lactonization steps under Lewis or Brønsted acid catalysis (vide infra).[14] However, achieving this process is thought to be somewhat difficult because of the known competitive oxa-Michael reaction[15] (Scheme 1).

Scheme 1. Concept of the Cascade Process



The feasibility of the projected hypothesis was examined by employing β-naphthol (**1a**) and ethyl 2-(6-oxocyclohex-1-en-1-yl)acetate (**2a**)[16,17] as substrates. Initially, we tested the reaction using Brønsted acids such as *p*-TSA, TFA, and TfOH in various solvents at different temperatures (Table S1).[16a,17] Among these, TfOH delivered bridged 2-chromanol lactone **3aa** as a single diastereomer in a moderate yield of 64% and 65% in ACN and DCE at 80 and 90 °C, respectively, over longer reaction times (entries 1 and 2). Next, we were curious to verify the effect of various Lewis acids in this transformation. Hence, several metal triflate catalysts such as $Sc(OTf)_3$, $Cu(OTf)_2$, AgOTf, $Zn(OTf)_2$, $Hg(OTf)_2$, and $Bi(OTf)_3$ were screened, and we found that Cu(II), Ag(I), and Hg(II) triflates were good catalysts by providing desired **3aa** in 52–84% yield (entry 3–7). Aiming at the identification of a more cost-effective and readily accessible catalytic system, some Fe-derived Lewis acids such as $FeCl_2$, $FeBr_2$, $FeBr_3$, $Fe(OTf)_2$, and $Fe(OTf)_3$ were tested (Table S1).[17] Gratifyingly, 20 mol % of $Fe(OTf)_3$ in DCE at 90 °C delivered the desired product **3aa** in the best isolated yield of 87% in 4 h (entry 8).[17] Further tuning of molar ratios of substrates, catalyst loading, temperature, and solvent did not lead to any noticeable progress in the yield of the tandem process (Table 1 and S1).[17] Reaction without the catalyst did not occur, and both starting materials (**1a** and **2a**) remained intact (entry 10). This observed high

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (20 mol %)	solvent, temp (°C)	time (h)	yield (%)[b]
1	TfOH	ACN, 80	24	64
2	TfOH	DCE, 90	8	65
3	$Cu(OTf)_2$	DCE, 90	8	68
4	AgOTf	toluene, 90	24	52
5	AgOTf	PhF, 90	8	81
6	AgOTf	DCE, 90	4	84
7	$Hg(OTf)_2$	DCE, 90	4	75
8	$Fe(OTf)_3$	DCE, 90	4	87
9	$Fe(OTf)_3$	PhF, 90	8	73
10[d]	no catalyst	DCE, 90	24	*c*
11	$Fe(OTf)_3$	DCE, 90	8	*e*

[a]Reaction conditions unless otherwise specified: **1a** (0.55 mmol), **2a** (0.55 mmol), and catalyst (20 mol %). [b]Isolated yields of **3aa**. [c]**1a** and **2a** were recovered. [d]Control experiment. Tf = triflate (CF_3SO_2). [e]*p*-Nitrophenol was used instead of **1a**.

activity (σ- and π-Lewis acid character) of $Fe(OTf)_3$ catalyst can be attributed to its resonance-stabilized triflate counterions ($CF_3SO_3^-$).[16b,c] Due to its high reactivity, stability, natural abundance, and cost-effectiveness, $Fe(OTf)_3$ was chosen as a prominent catalyst for this work (entry 8) instead of closely competent AgOTf and $Hg(OTf)_2$ (entries 6 and 7) (Table 1).[17]

With the optimal conditions established, the substrate scope with respect to the synthesis of bridged 2-chromanol-lactones **3** from **1** and **2** was initially explored. The reaction of **2a** with 6-bromonaphthalen-2-ol (**1b**) furnished **3ba** in 70% yield. Naphthalene-2,6-diol (**1c**) reacted with 1 equiv and 2 equiv of **2a** to afford **3ca** and **3ca′** in good yields of 76 and 75%, respectively. Naphthalen-1-ol (**1d**) was also found to be a good substrate and delivered **3da** in 62% yield. Other hydroxy arenes such as [1,1′-biphenyl]-4-ol (**1e**), 4-adamantylphenol (**1f**), 3,4-dimethoxyphenol (**1g**), and 4-methoxyphenol (**1h**) with **2a** furnished the corresponding products **3ea–ha** in 42–62% yield. Next, the reactivity of ethyl 2-(5-methyl-6-oxocyclohex-1-en-1-yl)acetate (**2b**) (α-methylated analogue of **2a**) with hydroxy arenes **1a**, **1b**, and **1d** was verified, which furnished **3ab**, **3bb**, and **3db** in good yields (56–66%). The cycloheptenone bearing keto-ester (ethyl 2-(7-oxocyclohept-1-en-1-yl)acetate (**2c**)) also proceeded smoothly and delivered products **3ac**, **3bc**, **3dc**, **3fc**, **3gc–gc′** (mixture), and **3hc** in good yields. As expected, electron-deficient *p*-nitrophenol, *p*-bromophenols, and basic N-protected *p*-aminophenols did not participate in the reaction with **2a**, where starting materials were fully recovered. Interestingly, using cyclopentenone derived keto-ester (ethyl 2-(5-oxocyclopent-1-en-1-yl)acetate (**2d**)) in reaction with hydroxy arenes **1a** and **1d** gave **3ad** and **3dd**, respectively, in moderate yields, which is in contrast with the previous observation of arrest of the reaction after Friedel–Crafts alkylation step of the similar cascade process (Scheme 2).[11,17]

To our delight, an unusual conglomerate (enantiomerically pure polymorph)[18] of **3ac** was obtained through crystallization using dichloromethane and petroleum ether (9:1) mixture. The single-crystal X-ray diffraction analysis of this conglom-

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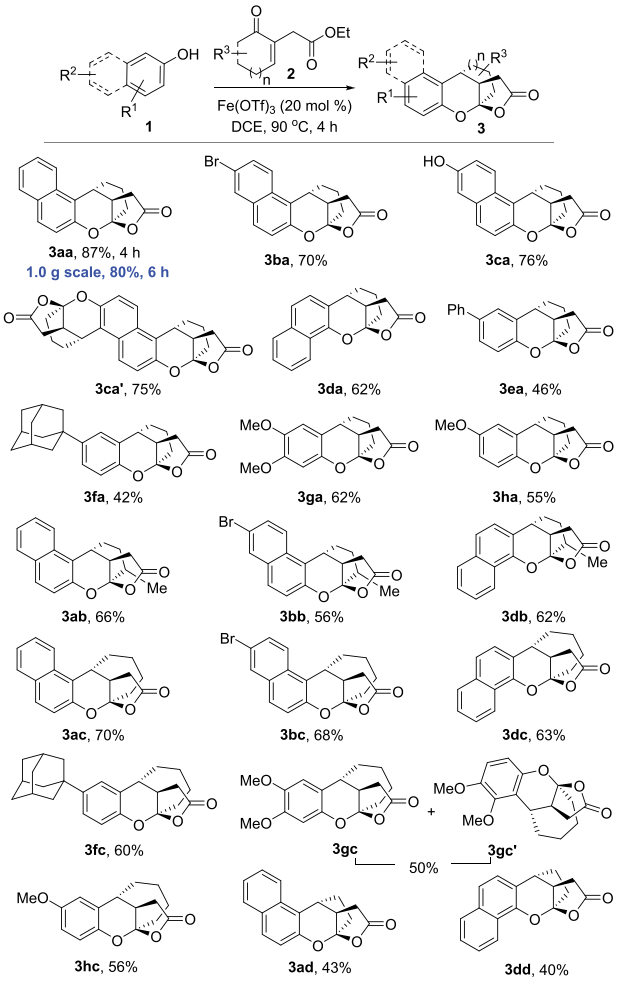
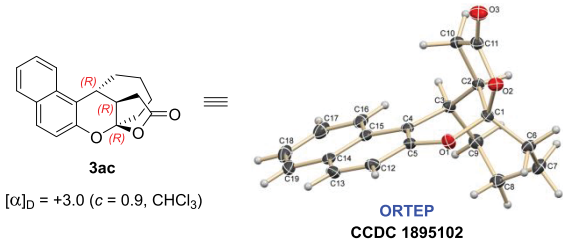
Scheme 2. Synthesis of Fused 2-Chromanol Lactones 3[a,b]



[a]All reactions were performed with 1.0 equiv of compounds **1** and **2** on a 0.55 mmol scale. [b]Isolated yields.

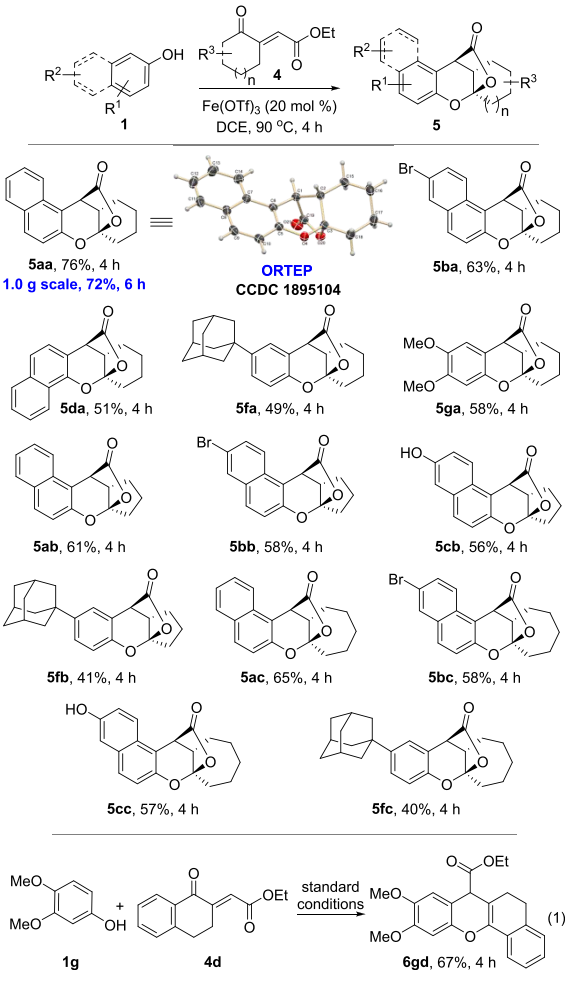
erate clearly established that the compound **3ac** has the *R* configuration at the C1, C2, and C3 positions (ORTEP numbering), and enantiomeric purity was further evaluated by chiral-HPLC analyses.[17] The structure and relative stereochemistry of all other products were established by analogy (Scheme 3).

Scheme 3. ORTEP of Conglomerate Crystal of 3ac



Encouraged by these results, we continued further to verify the scope of the reaction of hydroxy arenes **1** and keto-esters **4** (possessing ethyl (*E*)-4-oxopent-2-enoate motif),[19] which would deliver distinctively bridged 2-chromanol lactones **5**. To our delight, the reaction of **1a** with **4a** under optimized conditions gave **5aa** as a single diastereomer in a good yield of 76%. In order to verify the substrate scope, various hydroxy naphthalenes (**1b** and **1d**) and substituted phenols (**1f** and **1g**) were treated with keto-ester **4a** to give the corresponding cascade products **5ba**–**ga** in good yields of 49–63%. The cyclopentenone-derived keto-ester (ethyl (*E*)-2-(2-oxocyclopentylidene)acetate) **4b** also participated in the reaction with hydroxy arenes **1a**–**c** and **1f** and furnished the desired products **5ab**–**cb** and **5fb**, respectively. Similarly, the reaction of cycloheptanone-derived keto-ester **4c** with diverse hydroxy arenes delivered the corresponding adducts (**5ac**–**cc** and **5fc**) in good yields. Interestingly, the reaction of 3,4-dimethoxyphenol (**1g**) with tetralone-derived keto-ester **4d** under standard conditions gave the tetracyclic chroman **6gd** via an unusual Friedel–Crafts alkylation–ketalization–dehydration cascade. As we encountered in Scheme 2, a similar effect of the electronic nature of hydroxy arenes was noticed in these transformations. The isolated yields of products in Schemes 2 and 4 clearly indicate the superior reactivity of keto-esters **2** over **4**. The structure and relative stereochemistry of **5aa** were rigorously established by single-crystal X-ray analysis, and the remaining products were confirmed by analogy (Scheme 4).[17] Moreover, the synthetic utility of this cascade process was highlighted by conducting gram-scale experiments

Scheme 4. Synthesis of 2-Chromanol Lactones 5 and ORTEP of 5aa[a,b]



[a]All reactions were performed with 1.0 equiv of compounds **1** and **4** on a 0.55 mmol scale. [b]Isolated yields.

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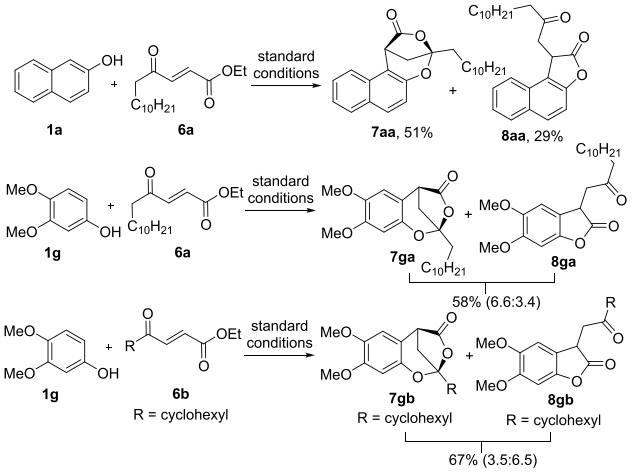
using 5.49 mmol (1.0 g scale) of **2a** and/or **4a** with **1a**, which proceeded smoothly and gave the corresponding products **3aa** (Scheme 2) and **5aa** (Scheme 4) in comparable yield.

After successful synthesis of diverse bridged 2-chromanol lactones **3** and **5**, we were curious to verify the reaction of hydroxy arenes **1** with keto-esters **6** (ethyl (*E*)-4-oxopent-2-enoates) possessing acyclic ketone functionality.[16] Thus, the reaction of **1a** with keto-ester **6a** was performed, which delivered the expected [3,2,1]-bridged ketal lactone **7aa** along with functionalized naphtho[2,1-*b*]furan-2(1*H*)-one **8aa** in 51% and 29% yield, respectively. Similarly, hydroxy arene **1g** with **6a** gave **7ga** and **8ga** in a 6.6:3.4 ratio. The cyclohexane-substituted keto-ester **6b** also well participated in the reaction with **1g** and furnished **7gb** and **8gb** in a 3.5:6.5 ratio and in good yields (Scheme 5).[17]

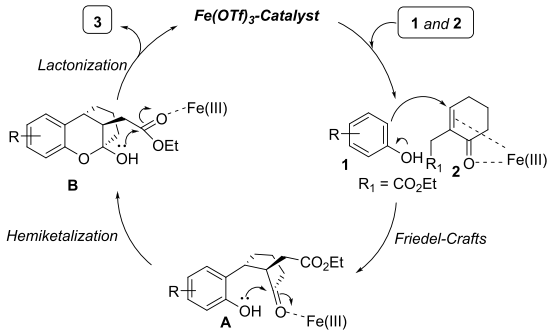
Scheme 5. Reactivity of Hydroxy arenes 1 with Ethyl (*E*)-4-Oxopent-2-enoates 6[a,b]



[a]$Fe(OTf)_3$ (20 mol %), **1** (1 equiv), and **6** (1 equiv) were used, and the reaction was carried out in DCE at 90 °C for 4 h. [b]Isolated yields.

While the precise reaction mechanism requires further investigation, a plausible mechanistic pathway based on earlier reports is presented (Scheme 6).[8,10−12] The reaction would be

Scheme 6. Plausible Reaction Mechanism



initiated by the activation of the enone **2** (σ- and π-activation) by Fe(III) catalyst to participate in a Friedel−Crafts-type reaction with hydroxyarene **1** (π-nucleophile) to give intermediate **A**. Fe(III)-facilitated diastereoselective intramolecular attack of the hydroxyl group of arene onto the activated carbonyl in **A** gives hemiketal **B**, which would undergo the subsequent intramolecular transesterification (lactonization) step to deliver the 2-chromanol lactone **3**. A similar mechanism can be postulated for the synthesis of 2-chromanol lactone **5** from **1** and **4**.

In conclusion, we have developed a facile and efficient Fe(III)-catalyzed cascade annulation of hydroxy arenes with diversely functionalized 4-keto esters that provides access to structurally complex doubly bridged polycyclic chromanol lactones through the formation of three new chemical bonds, two new rings, and three stereocenters. The cascade products are obtained in good yields with broad substrate scope using the cost-effective catalytic system. This protocol may find applications in diversity-oriented synthesis in medicinal chemistry and synthetic organic chemistry. Studies toward developing an enantioselective version of this reaction, evaluation of the biological profile of synthesized compounds, and crystallography studies on conglomerates of **3ac** are being carried out in our laboratory. The results will be published in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00614.

Experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1895102 and 1895104 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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