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Iron(III) Chloride Catalyzed Formation of 3,4-Dihydro-2*H*-pyrans from α-Alkylated 1,3-Dicarbonyls. Selective Synthesis of α- and β-Lapachone

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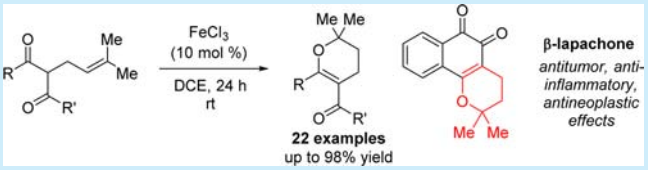
Supporting Information

ABSTRACT: A mild, catalytic method for the synthesis of 3,4-dihydro-2*H*-pyrans is described. The $FeCl_3$-catalyzed transformation of aryl- and alkyl β-diketones enables synthetic access to functionalized pyran core structures incorporated in many natural products and biologically active target structures. The method represents a mild alternative to currently available reaction protocols relying on stoichiometric reagents and harsh reaction conditions. This $FeCl_3$-catalyzed transformation has enabled the selective synthesis of α-lapachone in two synthetic transformations and subsequently β-lapachone in three synthetic transformations, which is currently undergoing clinical trials as a potent anticancer agent.



The pyran core structure is found in a wide variety of natural products and biologically active structures, such as coumarins,[1] flavonoids,[2] anthraquinones,[3] and numerous alkaloids.[4] Among the most abundant naturally occurring pyran moieties are tetrahydropyrans (**I**), tetrahydropyran-4-ones (**II**), 3,6-dihydro-2*H*-pyrans (**III**), and 3,4-dihydro-2*H*-pyrans (**IV**, Figure 1). Several synthetic strategies have been developed to access these versatile core structures within the past decades. In particular, Prins-cyclization reactions,[5] hetero-Diels–Alder reactions,[6] and intramolecular nucleophilic addition reactions[7] give rise to tetrahydropyran (**I**) and tetrahydropyran-4-one (**II**) subunits. Synthetic approaches toward 3,6-dihydro-2*H*-pyrans (**III**) involve formal [3 + 3] cycloaddition reactions[8] and 6π-electrocyclization reactions.[9] Figure 2 highlights common approaches toward the 3,4-dihydro-2*H*-pyran structural motif (**IV**) which include H_2SO_4- and $Hg(OTf)_2$-mediated isoprenoid cyclizations of farnesyl ketoesters such as **1**.[10] Additionally, prenylated β-ketoester **2** was reported to result in the formation of the corresponding 3,4-dihydro-2*H*-pyran product upon treatment with either stoichiometric $SnCl_4$[11] or catalytic I_2, PPh_3,[12] while the conversion of indanedione **3** in excess sulfuric acid proceeded in only low yields.[13] The majority of current strategies toward 3,4-dihydro-2*H*-pyrans (**IV**) rely on cycloaddition reactions of enolizable 1,3-diketones[14] in the presence of superstoichiometric amounts of either a Brønsted or Lewis acid (Figure 2). Alternatively, 3,4-dihydropyrans can be synthesized via radical cyclization involving an aldehyde and two alkenes.[15] We were interested in developing an approach to these useful motifs that would be sufficiently mild for application in complex molecule synthesis, particularly at a late stage. Herein we describe a mild method for the synthesis of functionalized 3,4-dihydro-2*H*-pyrans from both aryl- and alkyl-β-ketoesters **4** (Figure 4) relying on iron(III) chloride as a Lewis acid catalyst. At the outset

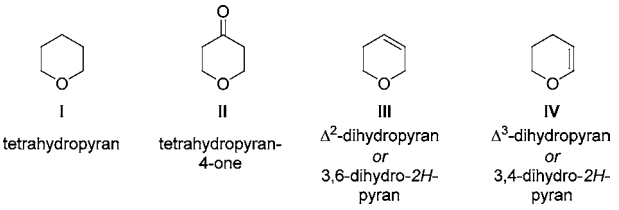


Figure 1. Common, naturally occurring pyran core structures.

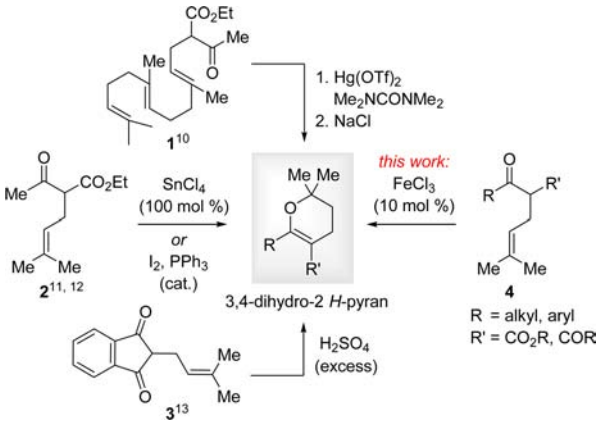


Figure 2. Carbonyl cyclization strategies toward 3,4-dihydro-2*H*-pyrans.

of our investigations, we focused on the evaluation of suitable Lewis acid catalysts for the intramolecular O-alkylation of both phenyl-β-ketoester **5** and methyl-β-ketoester **2** to the corre-

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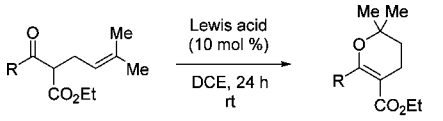
Table 1. Optimization of Reaction Conditions



R = Ph (**5**); Me (**2**) R = Ph (**6**); Me (**7**)

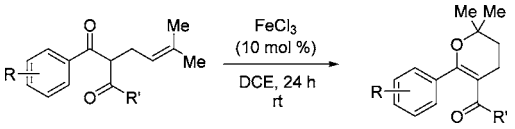
entry	R	Lewis acid	solvent	concn	yield (%)
1	Ph	$SnCl_4$ (10 mol %)	DCE	0.1 M	83
2	Me	$SnCl_4$ (10 mol %)	DCE	0.1 M	78
3	Ph	$BF_3{\cdot}Et_2O$ (10 mol %)	DCE	0.1 M	71
4	Me	$BF_3{\cdot}Et_2O$ (10 mol %)	DCE	0.1 M	78
5	Ph	$AlCl_3$ (10 mol %)	DCE	0.1 M	10
6	Ph	$Sc(OTf)_3$ (10 mol %)	DCE	0.1 M	81
7	Me	$Sc(OTf)_3$ (10 mol %)	DCE	0.1 M	62
8	Ph	$GaCl_3$ (10 mol %)	DCE	0.1 M	72
9	**Ph**	**$FeCl_3$ (10 mol %)**	**DCE**	**0.1 M**	**95**
10	**Me**	**$FeCl_3$ (10 mol %)**	**DCE**	**0.1 M**	**93**
11	Ph	$FeCl_3$ (10 mol %)	DCM	0.1 M	69
12	Me	$FeCl_3$ (10 mol %)	DCM	0.1 M	73
13	Ph	$FeCl_3$ (10 mol %)	toluene	0.1 M	65
14	Me	$FeCl_3$ (10 mol %)	toluene	0.1 M	74
15	Ph	$FeCl_3$ (10 mol %)	DCE	0.01 M	72
16	Ph	$FeCl_3$ (5 mol %)	DCE	0.1 M	48
17	Ph	$Fe(OTf)_3$ (10 mol %)	DCE	0.1 M	77
18	Me	$Fe(OTf)_3$ (10 mol %)	DCE	0.1 M	28

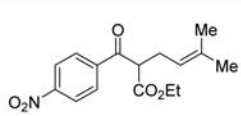
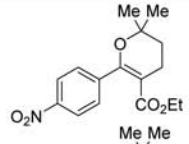
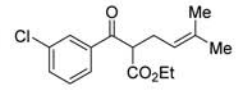
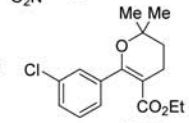
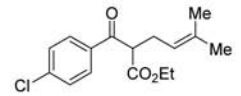
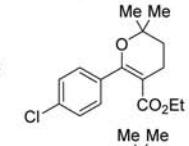
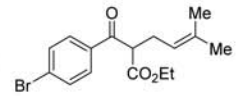
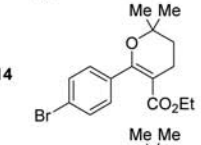
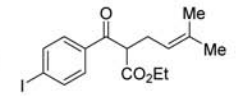
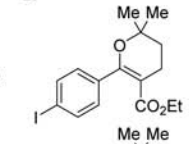
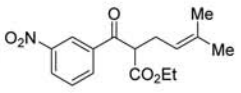
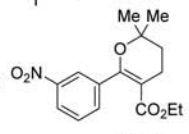
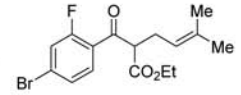
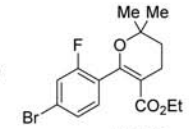
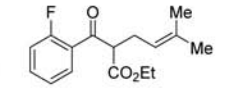
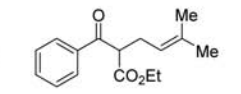
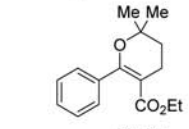
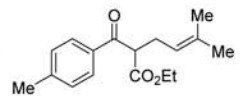
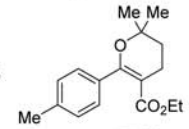
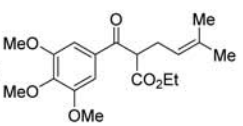
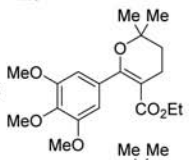
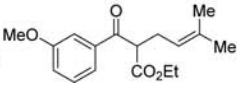
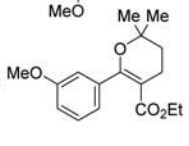
[a]All reactions were performed using β-ketoesters **2** or **5** at rt for 16–24 h. [b]Yield determined by ^{1}H NMR using naphthalene as an internal standard. See Supporting Information for more details.

sponding 3,4-dihydropyrans (Table 1). We initially turned our attention to $SnCl_4$ which has been reported to catalyze the intramolecular α-alkylation of prenylated carbonyl compounds via the formation of tin-enolate intermediates.[16] Based on this literature precedent, we envisioned a design principle in which metal-enolates are key intermediates in enabling subsequent O-alkylation to form the desired 3,4-dihydro-2*H*-pyrans under catalytic conditions.

When a catalytic amount of $SnCl_4$ (10 mol %) was reacted with phenyl-β-ketoester **5**, the formation of the desired 3,4-dihydro-2*H*-pyran **6** was observed in 83% yield while methyl-β-ketoester **2** formed **7** in 78% yield under identical reaction conditions (entries 1–2, Table 1). The use of $BF_3{\cdot}Et_2O$[17] as a stronger Lewis acid resulted in the formation of pyrans **6** and **7** in comparable yields (entries 3–4, Table 1) while the use of $AlCl_3$ as a more potent Lewis acid[18] resulted in the formation of the desired pyran **6** in greatly diminished yields of 10% (entry 5, Table 1). Conversion of β-ketoesters **2** and **5** with $Sc(OTf)_3$ and $GaCl_3$ provided results comparable to those obtained with $SnCl_4$ and $BF_3{\cdot}Et_2O$ while no product formation was observed with a variety of other Lewis acids (e.g., $FeCl_2$, $ZnCl_2$, $Zn(OTf)_2$). Our succeeding investigations found $FeCl_3$ to be a superior Lewis acid capable of catalyzing the desired reaction, transforming both phenyl-β-ketoester **5** and methyl-β-ketoester **2** in high yields of 95% and 93% to the corresponding 3,4-dihydro-2*H*-pyrans **6** and **7** (entries 9–10, Table 1). Ultimately, we identified 10 mol % $FeCl_3$ in dichloroethane at ambient temperatures as the optimal set of reaction conditions while other solvents and lower catalyst loadings and concentrations resulted in diminished yields (entries 11–16, Table 1; see Supporting Information for more details). The optimized reaction conditions proved efficient for a variety of substrates bearing both aryl- and alkyl-ketone substituents (Tables 2 and 3). Aromatic esters bearing

Table 2. Substrate Scope for Aryl-β-ketoesters[a]



entry	substrate		product		yield (%)
1		**8**		**9**	98
2		**10**		**11**	90
3		**12**		**13**	85
4		**14**		**15**	69
5		**16**		**17**	74
6		**18**		**19**	95
7		**20**		**21**	91
8		**22**		**23**	85
9		**5**		**6**	95
10		**24**		**25**	50
11		**26**		**27**	21
12		**28**		**29**	66

[a]All reactions were performed using 0.2 mmol of β-ketoester, 0.02 mmol of Lewis acid $FeCl_3$ in DCE (0.1 M) at rt for 16–26 h.

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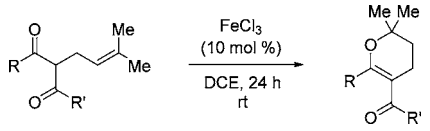
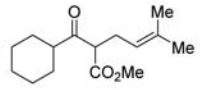
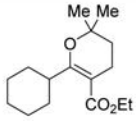
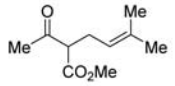
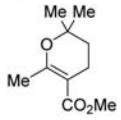
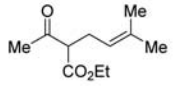
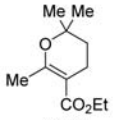
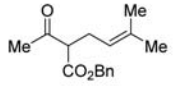
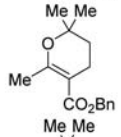
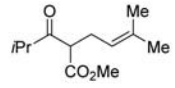
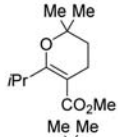
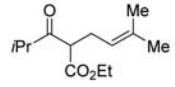
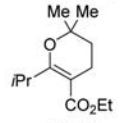
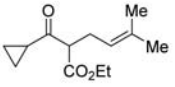
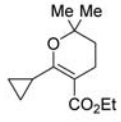
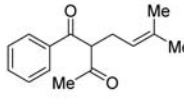
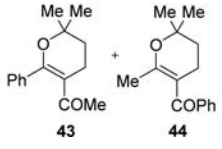
Table 3. Substrate Scope for Alkyl-β-ketoesters and α-Alkylated 1,3-Diketones[a]



entry	substrate		product		yield (%)
1		30		31	72
2		32		33	50
3		2		7	75
4		34		35	60
5		36		37	40
6		38		39	54
7		40		41	56
8		42		43 / 44	41 (43) / 34 (44)

[a]All reactions were performed using 0.2 mmol of β-ketoester, 0.02 mmol of Lewis acid $FeCl_3$ in DCE (0.1 M) at rt for 1−48 h.

electron-deficient nitro-, chloro-, bromo-, and iodoarenes were converted to the corresponding 3,4-dihydro-2*H*-pyrans in good to excellent yields (entries 1−7, Table 3). Electron-donating substituents on the arene moiety resulted in the formation of the desired pyran products albeit in lower yields (entries 10−12, Table 2). We next sought to expand the scope of the $FeCl_3$-catalyzed formation of 3,4-dihydro-2*H*-pyrans to alkyl-β-ketoesters and α-alkylated 1,3-diketones. Sterically demanding cyclo hexyl, cyclopropyl, and isopropyl substituents were well tolerated on the ketone subunit and provided the desired products in good yields (entries 1, 5−7, Table 3). Methyl-, ethyl-, and benzylester functionalities resulted in the formation of the corresponding 3,4-dihydro-2*H*-pyrans in good yields (entries 1−7, Table 3). However, the reaction of α-prenylated 1,3-diketone **42** led to the formation of a mixture of pyran products **43** and **44** in 41% and 34% yield, respectively. When tetra-alkyl substituted and styrene derivatives were subjected to the reaction conditions, no formation of the desired pyran products was observed. A mechanistic hypothesis consistent with the results obtained is postulated in Figure 3. The iron-enolate intermediate **46** is

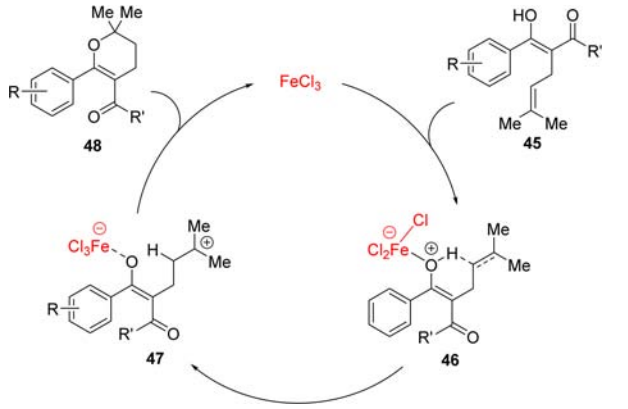


Figure 3. Mechanistic hypothesis for the $FeCl_3$-catalyzed formation of 3,4-dihydro-2*H*-pyrans.

formed upon coordination of $FeCl_3$ to the carbonyl-oxygen of enol **45**.[19] The isoprenyl moiety in **46** is then protonated via an intramolecular proton transfer to form carbocation intermediate **47** which subsequently undergoes *O*-alkylation with the enolate nucleophile to form the desired pyran product **48**. Alternatively, $FeCl_3$ can bind to the isoprenyl fragment to activate it for subsequent nucleophilic attack of the carbonyl oxygen to result in the formation of 3,4-dihydro-2*H*-pyran **48**. Subsequent efforts focused on the synthesis of β-lapachone (**51**) from lapachol (**49**) in two synthetic transformations relying on our $FeCl_3$-catalyzed reaction conditions for the formation of 3,4-dihydro-2*H*-pyrans (Figure 4). β-Lapachone or ARQ 501[20] (**51**) is a naturally

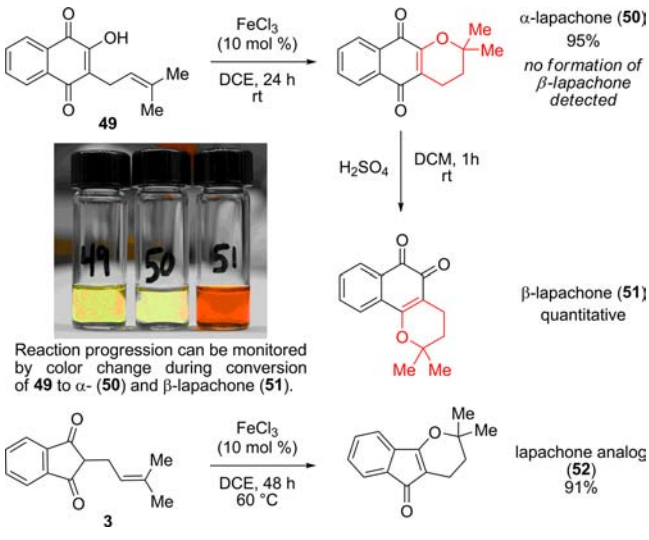


Figure 4. Synthesis of α-lapachone (**50**), β-lapachone (**51**), and its analog pyran (**52**).

occurring napthoquinone which shows promising activity as an anticancer agent and is currently undergoing multiple clinical trials in phases I and II. Previous syntheses of β-lapachone have been reported, relying on the conversion of lapachol (**49**) with stoichiometric Brønsted or Lewis acids, such as sulfuric acid and $NbCl_5$, and often form regiosiomeric mixtures of α-lapachone (**50**) and β-lapachone (**51**).[21] When lapachol (**49**) was treated under the optimized reaction conditions for the formation of 3,4-

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dihydro-2*H*-pyrans, we were able to isolate the desired product α-lapachone (**50**) as a single regioisomer in 95% yield. Importantly, no formation of β-lapachone (**51**) was detected. However, when α-lapachone (**50**) was subjected to standard purification techniques using column chromatography, we observed conversion of α-lapachone (**50**) to β-lapachone (**51**). In subsequent studies, we achieved complete isomerization of α-lapachone (**50**) to β-lapachone (**51**) in quantitative yield upon subjection to sulfuric acid (1 h, room temperature, 25 equiv of H_2SO_4, 0.05 M in DCM). Nevertheless, direct conversion of lapachol (**49**) with sulfuric acid (room temperature, 25 equiv of H_2SO_4, 0.05 M in DCM, 1−24 h) was found to result in a complex mixture of both regioisomeric products, α-lapachone (**50**) and β-lapachone (**51**). Based on these results, we hypothesize that β-lapachone (**51**) could be an artifact observed upon isolation of the natural product α-lapachone (**50**) under mild acidic reaction conditions. Furthermore, this protocol for the $FeCl_3$-catalyzed formation of 3,4-dihydro-2*H*-pyrans proved efficient for the synthesis of β-lapachone analog **52** which had previously been obtained under Brønsted acid mediated reaction conditions in only 9% yield. Conversion of indanedione **3** with $FeCl_3$ (10 mol %) proceeded at elevated temperatures and prolonged reaction times to form lapachone analog **52** in 91% yield.[13] In summary, we have developed a mild synthetic method for the synthesis of functionalized 3,4-dihydro-2*H*-pyrans utilizing $FeCl_3$ as a Lewis acid catalyst. The method has enabled the selective synthesis of α-lapachone and regioisomer, β-lapachone, a promising anticancer agent in multiple phase II clinical trials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00254.

Experimental data as well as ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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