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Simple access to 5-carboalkoxy-2,3-dihydro-4*H*-pyran-4-ones *via* domino acylative electrocyclization: the first three step total synthesis of the dihydronaphthopyran-4-one class of natural products†

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Intermolecular domino C-acylation/6π-oxaelectrocyclization between β-ketoesters and α,β-unsaturated acid chlorides took place readily in the presence of $CaCl_2$ to afford a variety of polysubstituted 5-carboalkoxy-2,3-dihydro-4*H*-pyran-4-ones, in good yields. The products were successfully exploited as precursors, for a simple and efficient construction of a naphthalene fused pyran-4-one ring system. This intramolecular Friedel–Crafts acylative aromatization approach was useful for the synthesis of the phytogrowth-inhibiting dihydronaphthopyranone class of natural products.

Introduction

Linear naphthalene fused pyran-4-one ring systems, such as naphtho-γ-pyrone (**NGP**),[1] 1,4-pyranonaphthoquinone (**PNQ**),[2] and bisnaphthopyranone (**BNP**)[3] containing compounds are well known fungal metabolites. Some of the natural products rubrofusarin B (**i**),[1e–g] 4-oxo-α-lapachone (**ii**),[2d,e] cephalochromin,[3a,b] chaetochromin A[3c] and nigerone[3d,e] belonging to this class exhibit important biological activities such as topoisomerase-II inhibition, toxin inhibition, anti-tumour, anti-bacterial and anti-proliferative activity. Similarly, linear dihydronaphthopyran-4-one (**DHNP**) natural products,[4] *trans*-**11b**, *cis*-**11b** and **11c** showing phytogrowth-inhibition activity, constitute another important sub-class of naphthalene fused pyran-4-ones. The presence or absence of a double bond in the pyranone ring and the hydroxyl or the 1,4-diketone functionality in the adjacent naphthalene ring gives rise to structural differences (Fig. 1).

Although there are methods known for the synthesis of different naphthopyran-4-one class of compounds (**B**, Scheme 1a),[1–3] the synthesis of **DHNP** class of natural products,[4] (**D**, Scheme 1b) remains virgin. These approaches are either based on construction of pyranone on a pre-existing naphthalene ring (**A**, Scheme 1a),[1–3] or reaction of orsellinate anion with pyrylium salt.[1g] Moreover, these methods are difficult to be adopted for the synthesis of **DHNPs** (ref. 4) because of drawbacks such as, difficulty in chemoselective conjugate reduction of enone in **NGP** (**B**, Scheme 1a), need for the use of hard to handle intermediates such as pyrylium salt[1g] and dimsyl anion,[3d,e] formation of mixture of products,[1g] and conversion of angular to linear naphthopyranone involving lengthy synthetic sequence.[3d,e] Thus there is a need for development of a new and efficient method for the synthesis of **DHNPs**.

Designing simple but powerful domino reactions useful for construction of cyclic ring systems, especially natural products, is a challenging task.[5] Strategic positioning of functional groups in a molecule allows tandem reactions to take place in one pot. Considering the advantages of domino reactions, and to overcome the drawbacks mentioned above, we envisaged to generate naphthalene fused dihydropyran-4-one ring system (**D**, Scheme 1b) in a shortest possible way, by intramolecular Friedel–Crafts acylative aromatization of 6-benzyl-5-

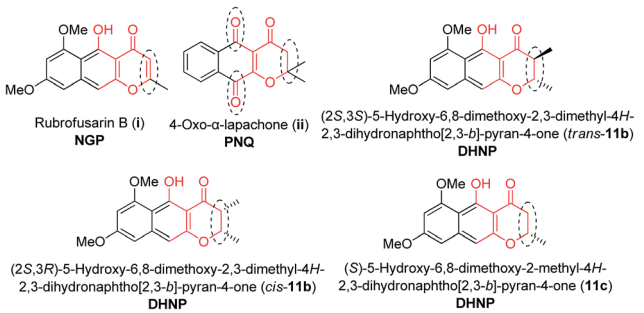

Fig. 1 Linear naphthopyran-4-one class of natural products.

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† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra for all compounds and X-ray structural information of **3ga** (CIF). CCDC 1019144. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra11174e

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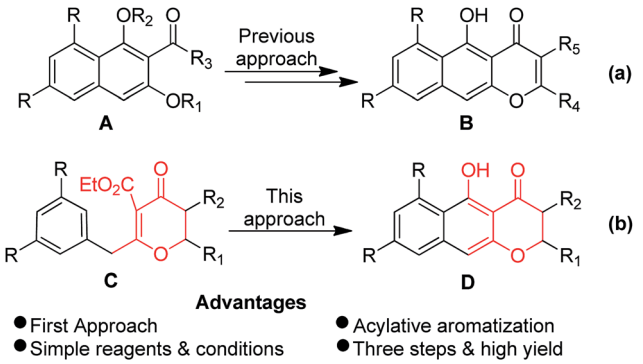

Scheme 1 Approaches for naphthopyran-4-one ring formation.

carboalkoxy-2,3-dihydropyran-4-one (**6-BCDHP**, **C**, Scheme 1b), which in turn could be generated *via* domino C-acylation/6π-oxaelectrocyclization reaction between β-ketoesters and α,β-unsaturated acid chlorides.

Literature background shows that synthesis of 6-alkyl/aryl-5-carboalkoxy-2,3-dihydropyran-4-ones (**6-ACDHPs**) was reported independently by Gelin[6a] and Takeda[6b] as well as used as intermediate in the synthesis of natural products.[6b,7] Nevertheless, these methods does not cover synthesis of **6-BCDHP** and has drawbacks such as need for the use of stoichiometric quantity of bases such as $Mg(OEt)_2$ (ref. 6a) and NaH,[6b] high reaction temperature and limited substrate scope. Also, other methods known for the synthesis of substituted 2,3-dihydropyran-4-one (**DHP**) ring system without 5-carboalkoxy substituent was found not suitable for the synthesis of 5-carboalkoxy-2,3-dihydropyran-4-one (**5-CDHP**).[8–16] The presence of 5-carboalkoxy group in **DHP** ring system provides multitude of opportunities for further synthetic transformations. Thus we realised that development of a simple method for the synthesis of **6-ACDHP** itself is desirable. To avoid the use of stoichiometric quantity of base,[6] in C-acylation of β-keto esters with α,β-unsaturated acid chloride, to get **DHPs**, we thought of using a Lewis acid. Lewis acids are expected to work in catalytic quantity for the C-acylation reaction.[17] $CaCl_2$ is a biocompatible, cost-effective, bifunctional (Lewis acid as well as Lewis base) catalyst and it has been exploited only to limited extent in organic synthesis,[18a,b] for example, in aldol reaction,[18c] Biginelli reaction,[18d] synthesis of Mannich bases,[18e] and aminophosphonic esters.[18f] Thus in continuation of our interest on the use of $CaCl_2$,[19] as Lewis acid catalyst we examined its utility in this reaction. Herein we present successful realisation of what we contemplated.

Results and discussion

Reaction optimization

To start with, reaction between ethylbenzoylacetate (**1a**) and 3,3-dimethylacrylolyl chloride (**2a**) was designed as a model, to check the feasibility of formation of 5-carboalkoxy-2,3-dihydro-4*H*-pyran-4-one (**3aa**, Table 1). When an equimolar mixture of **1a** and **2a** was stirred for 7 h at room temperature in the presence of $CaCl_2$ (5 mol%) and Et_3N (2.0 equiv.) in DCM, the expected dihydropyranone **3aa** was obtained only in 60% yield (Table 1, entry 1). Gratifyingly, the yield of product **3aa** improved to 80% when the quantity of the $CaCl_2$ was increased to 10 mol% (entry 1). Further, increasing the quantity of $CaCl_2$ to 20 mol% or decreasing the quantity of Et_3N did not improve the yield (entries 1 and 2). In the absence of Et_3N (entry 3) no reaction was observed and in the absence of $CaCl_2$ (entry 4) a mixture of product was formed.

Change of solvent to DMF, toluene and THF only lead to decrease in the yield (entry 5). Similarly, change of base to DMAP, DBU or DABCO had either decreased the yield or led to the formation of mixture of products (entries 6 and 7). Making use of other alkaline earth metal chlorides ($MgCl_2$ and $BaCl_2$) and transition metal halides ($ZnCl_2$, $FeCl_3$, $CuCl_2$ and $CeCl_3$) had only negative impact on the reaction (entries 8–12). Based on these results, treatment of an equimolar mixture of β-ketoester and α,β-unsaturated acid chloride in the presence of 10 mol% of $CaCl_2$ and 2.0 equiv. of Et_3N in DCM at room temperature (entry 1) was identified as the optimum condition for further study.

Substrate scope

With the optimal reaction condition in hand, scope and limitation of the reaction was explored using fourteen different β-ketoesters and six different α,β-unsaturated acid chlorides such as, 3,3-dimethylacryloyl chloride (**2a**, or senecioyl chloride), (*E*)-2,3-dimethylacryloyl chloride (**2b**, or tigloyl chloride), crotonoyl chloride (**2c**), acryloyl chloride (**2d**), cinnamoyl chloride (**2e**) and (*E*)-pent-2-enoyl chloride (**2f**, Scheme 2). Comparison of the reactivity of the different β-ketoesters (**1a–1d**) with 3,3-dimethylacryloyl chloride (**2a**) revealed that the electron donating substituents such as 4–Me, 4-OMe and 3,4,5-OMe on the aromatic ring had no significant effect on the rate and yield of the reaction. The presence of chloro group, at sterically hindered *ortho* position in the β-ketoester **1f** slowed down the reaction (see **3ea** and **3fa**) compared to *para* position in the β-ketoester **1e**. Among the different acid chlorides, **2a** gave high yield of the product (see **3aa**, *tc*-**3ab**, **3ac**) compared to **2b** and **2c**. The product *tc*-**3ab** was obtained as a separable *trans–cis* (*dr* 6 : 4) diastereomeric mixture, which was confirmed by ^{1}H NMR.

While thiophene and furan derived β-ketoesters, **1g** and **1h** gave the product **3ga** and **3ha** respectively in excellent yield, the expected product **3ia** could not be obtained with pyridine derived β-ketoester **1i**. Most likely, the pyridine nitrogen might have formed irreversible complex with acid chloride. Formation of **6-ACDHP** ring structure was further confirmed using the X-ray crystal structure obtained for the compound **3ga** (Fig. 2).[20] Acryloyl chloride (**2d**) and cinnamoyl chloride (**2e**) failed to react with **1a** to provide the desired product **3ad** and **3ae**. This is similar to the failure of α,β-unsaturated 1,3-diketones, which has no substitution or phenyl group substitution at β position, to undergo cyclization to form **DHPs**.[12]

Further, the substrate scope was extended to aliphatic β-ketoesters. The acid chlorides **2a** and **2c** on reaction with ethyl acetoacetate (**1j**) produced **3ja** and **3jc** respectively in good yield. Similarly, methyl-3-oxo-pentanoate (**1k**) on reaction with acid chlorides **2a** and **2b** gave the expected product **3ka** and **3kb**

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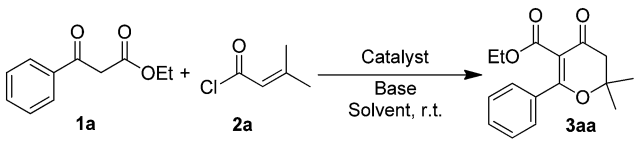
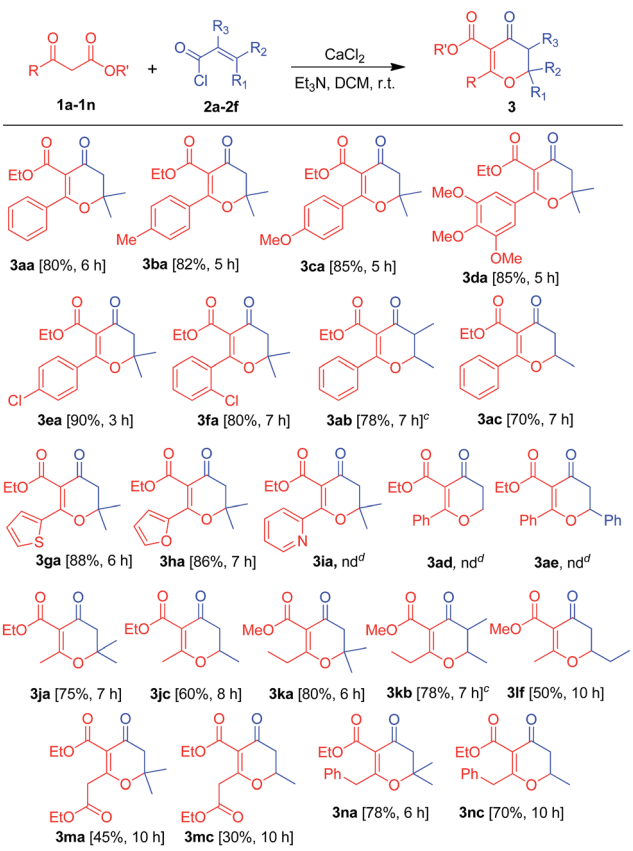
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (mol%)	Base	Solvent	Time (h)	Yield[b] (%)
1.	$CaCl_2$ (5), (10), (20)	Et_3N	DCM	7, 7, 7	60, 80, 80
2.	$CaCl_2$ (10)	Et_3N	DCM	7	70[c]
3.	$CaCl_2$ (10)	—	DCM	15	NR[d]
4.	—	Et_3N	DCM	15	nd[e]
5.	$CaCl_2$ (10)	Et_3N	DMF, toluene, THF	24	55, 40, 20
6.	$CaCl_2$ (10)	DMAP, DBU	DCM	24	30, 20
7.	$CaCl_2$ (10)	DABCO	DCM	24	nd[e]
8.	$MgCl_2$ (20)	Et_3N	DCM	24	25
9.	$BaCl_2$ (20)	Et_3N	DCM	24	20
10.	$ZnCl_2$ (20)	Et_3N	DCM	24	15
11.	$FeCl_3$ (20)	Et_3N	DCM	24	nd[e]
12.	$CuCl_2$ (20), $CeCl_3$ (20)	Et_3N	DCM	24	Trace

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), base (2.0 mmol) and solvent (5 mL) at room temperature. [b] Isolated yield. [c] 1.5 equiv. of Et_3N was used. [d] NR = no reaction (β-ketoester **1a** was recovered). [e] Not determined.



Scheme 2 Synthesis of 5-carboalkoxy-2,3-dihydro-4*H*-pyran-4-ones. [a]Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), $CaCl_2$ (0.1 mmol), triethylamine (2.0 mmol) in DCM (5 mL) at room temperature. [b]Isolated yield. [c]*trans*–*cis* = 6 : 4 was confirmed by ^{1}H NMR of crude reaction mixture. [d]Not determined.

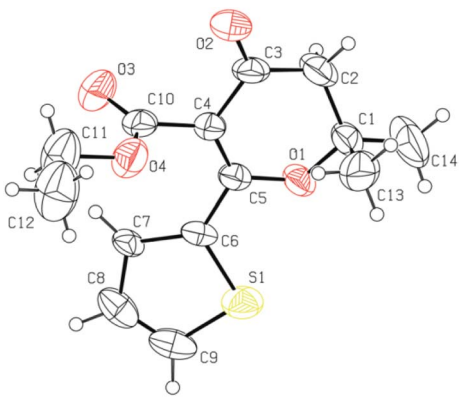
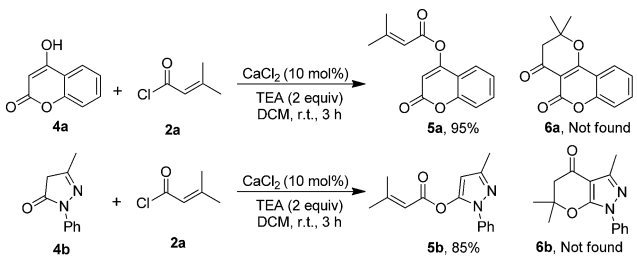


Fig. 2 ORTEP diagram of compound **3ga**.

respectively in very good yield. Compound **3lf**, a potential intermediate for the synthesis of the natural product hepialone[21] was obtained in moderate yield when compound **1l** was treated with acid chloride **2f**. Dihydropyranones **3ma** and **3mc**



Scheme 3 $CaCl_2$ catalyzed C-acylation *vs.* O-acylation of cyclic active methylene compounds.

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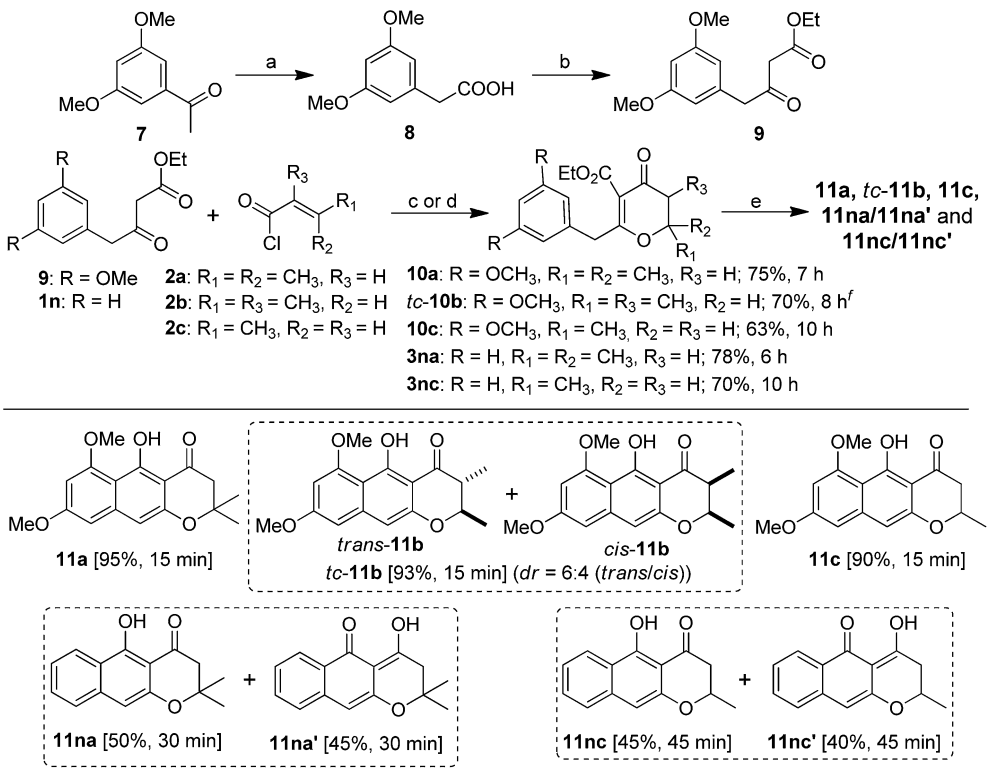
were obtained in moderate yield from the reaction of diethyl acetone dicarboxylate (**1m**) with acid chlorides **2a** and **2c**. Interestingly, **6-BCDHPs**, **3na** and **3nc**, useful intermediates for the synthesis of **DHNPs 8na** and **8nc** (Scheme 4), was obtained in good yield starting with ethyl 3-oxo-4-phenylbutyrate (**1n**). Thus, the domino acylative cyclization method was found useful for the synthesis of wide variety of polysubstituted **6-ACDHPs** including **6-BCDHPs**.

Under the optimized condition, reaction of cyclic active methylene compounds such as 4-hydroxycoumarin (**4a**) and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**4b**) with 3,3-dimethylacryloyl chloride (**2a**) was examined (Scheme 3). However, similar to the formation of O-acylated product in the case of Lewis acid, $SmCl_3$,[17] only O-acylated products **5a** (ref. 17) and **5b** were obtained in good yield in the presence of $CaCl_2$. Increasing the temperature or the catalyst did not change the course.

Total synthesis of dihydronaphthopyran-4-one (DHNP) class of natural products and its analogs

As a part of our strategy, utility of **6-BCDHPs**, **3na**, **3nc** and **10a-c**, was examined as starting materials, for the synthesis of **DHNP** class of synthetic analogs **11na**, **11nc** and **11a**, and natural products *trans*-**11b**, *cis*-**11b** and **11c**. On treatment with PPA compounds **3na** and **3nc** (Scheme 2 and 4) underwent facile intramolecular Friedel–Crafts acylative aromatization to afford a separable mixture of **11na** (50%)/**11na′** (45%) and **11nc** (45%)/**11nc′** (40%) respectively in very high yield (Scheme 4). As a next step, synthesis of β-keto ester **9**, starting material for the synthesis of **11a**, *trans*-**11b**, *cis*-**11b** and **11c** was initiated. 3,5-Dimethoxyacetophenone (**7**) was subjected to Willgerodt–Kindler reaction to get 3,5-dimethoxyphenyl acetic acid (**8**) in very good yield. Compound **8** was further coupled with Meldrum's acid using DCC/DMAP and refluxed with ethanol to get the β-ketoester **9**. However, when compound **9**, containing 3,5-dimethoxy benzene ring, was treated with acid chloride **2a**, under the standard reaction condition using $CaCl_2$, a mixture of products, instead of the desired product **10a**, was obtained. There was no change in the course of the reaction when the reaction temperature was lowered or increased; quantity of $CaCl_2$ was increased to 1.0 equiv.; solvent was changed to DMF. Similarly, when the reaction was tried with different Lewis acids such as $Yb(OTf)_3$, $In(OTf)_3$, $Cu(OTf)_2$, $SmCl_3$ (ref. 17) and $InCl_3$ an inseparable mixture of unidentifiable products was obtained. Thus we were bewildered to know that, while compound **1n** could give rise to cyclised product **6-BCDHP** (**3n**), compound **9** failed to give the desired product **10a** in the presence of Lewis acids. Most likely, the electron rich 3,5-dimethoxy benzene ring, in the presence of Lewis acid, may undergo side reactions and play spoilsport. To overcome this problem in the preparation of compound **10a** and to achieve our main goal of synthesis of compound **11a–c**, we opted to use a base, $Mg(OEt)_2$,[6a] instead of Lewis acid. To our delight, with



Scheme 4 Total synthesis of dihydronaphthopyranone class of natural products and its analogs. [a]Reagents and conditions: (a) S_8, TsOH/morpholine, 120–130 °C, 6 h; 20% aq. NaOH, TBAB, 100–110 °C, 6 h, 80%; (b) Meldrum's acid, DCC, DMAP, DCM, 25 °C, 5 h; EtOH, reflux, 10 h (50% for two steps); (c) **9**, $Mg(OEt)_2$, dry toluene, 100 °C, 30 min; **2** (**2a–c**), ACN, r.t.; (d) **3n** and **2** (**2a** and **2c**), $CaCl_2$, Et_3N, DCM, r.t.; (e) PPA, 80 °C; [f]*trans*–*cis* = 6 : 4 was confirmed by ^1H NMR of crude reaction mixture.

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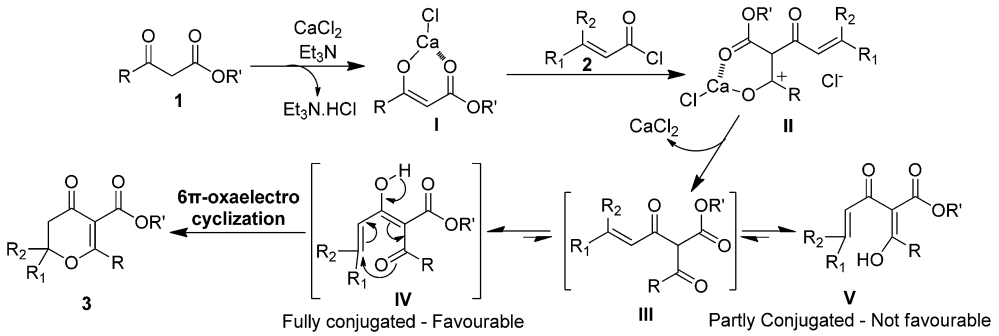

Scheme 5 Proposed mechanism.

$Mg(OEt)_2$ a facile acylation followed by 6π-oxaelectrocyclization took place readily to deliver dihydropyranone **10a**. Similarly, other dihydropyranone derivatives *tc*-**10b** and **10c** were prepared in good yield using $Mg(OEt)_2$.

Further, **6-BCDHPs 10a**, *tc*-**10b** and **10c** were successfully converted to **DHNPs 11a**, *tc*-**11b** and **11c** respectively, in excellent yield by following the procedure used for the conversion of compound **3na**. The product *tc*-**11b** was obtained as a separable diastereomeric mixture of *trans*-**11b** and *cis*-**11b** isomer (*dr* 6 : 4). The constrained *cis*-geometry of the ester group favoured aromatic acylation. This forms the first ever, short, three step total synthesis of naturally occurring dihydronaphthopyranones *trans*-**11b**, *cis*-**11b** and **11c** and its synthetic analogs **11a**, **11na**, **11na′**, **11nc** and **11nc′**.

Mechanistic hypothesis

Based on our own observations and previous literature precedence,[12,17] a plausible reaction mechanism for the formation of 5-carboalkoxy-2,3-dihydropyran-4-one (**3**) is proposed (Scheme 5). The *in situ* generated γ,δ-unsaturated β-diketone (**III**) is expected to exist in fully conjugated and more stable enolic form **IV**,[12] instead of partly conjugated and less stable enolic form **V**. Intermediate **III** might undergo 6π-oxaelectrocyclization instead of intramolecular oxa-Michael addition to form the product **3**. The acid chlorides **2a**, **2b**, **2c** and **2f** substituted with alkyl groups at β-position reacted efficiently while **2d** with no substitution and **2e** with phenyl substitution failed to react. This shows that dialkyl or mono alkyl substituents at β-position of the acid chloride favours positive polarization for the 6π-oxaelectrocylization[12] to take place.

This mechanism is further supported by the observation that the cyclic active methylene compounds (**4a** and **4b**) did not undergo pyranone ring formation. These compounds are well known to exist in the enol form, thus the geometric constraints may not allow the catalyst to achieve cyclic coordination state similar to **I**. Thus, O-alkylation rather than C-alkylation took place.

Conclusions

In conclusion, we have developed a simple and efficient domino strategy for the synthesis of polysubstituted 5-carboalkoxy-2,3-dihydro-4*H*-pyran-4-ones from acyclic β-ketoesters and α,β-unsaturated acid chloride in the presence of $CaCl_2$. Unlike the need for the stoichiometric quantity of bases such as $Mg(OEt)_2$ and NaH, the Lewis acid $CaCl_2$ worked effectively in catalytic quantity. The 6-benzyl-5-carboalkoxy-2,3-dihydro-4*H*-pyran-4-ones were successfully employed as intermediates for the first and concise total synthesis of dihydronaphthopyranone class of natural products and its synthetic analogs *via* intramolecular Friedel–Crafts acylative aromatization. This *in situ* generation of naphthalene ring system has potential for its extension to the synthesis of other naphthopyran-4-one class of compounds such as **NGP**, **PNQ** and **BNP**. Investigation in this direction is under progress in our laboratory. Also, studies on acylation of 1,3-diketones using the same strategy is under progress so that we did not present the results in this manuscript.

Experimental section

General remarks

Melting points were determined by the open capillary tube method using a Toshniwal melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance 400 (400 MHz) NMR spectrometer. Chemical shifts are reported in ppm (δ) relative to internal standard tetramethylsilane (TMS, δ 0.00 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad resonance (br)], coupling constants [Hz], integration). All the NMR spectra were acquired at ambient temperature. ESI-MS was recorded on Agilent 1100 LC/MSD (70 eV) spectrometer. High resolution mass spectra (HRMS) were recorded on a Waters Q-Tof micro mass spectrometer. Elemental analyses were performed on a CHN analyser. X-ray crystallographic data were collected on a Bruker SMART APEX-II CCD diffractometer. Thin layer chromatography (TLC) was performed on Merck pre-coated silica gel 60F plates and visualized by exposure to UV light. ACME silica gel (100–200 mesh) was used for column chromatography. All commercially available reagents were used without purification unless otherwise indicated and were purchased from standard chemical supplier. The β-ketoesters **1b–1i**,[22] and **1n** (ref. 23) was prepared according to literature procedure. Polyphosphoric acid (Sigma-Aldrich: catalogue no.: 208213) reagent grade, 115% H_3PO_4 basis was used for the reaction.

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General method A: typical experimental procedure for the synthesis of 2,3-dihydro-4*H*-pyran-4-ones (3)

To a suspension of β-ketoester (**1**, 1.0 mmol), $CaCl_2$ (0.1 mmol) and Et_3N (2.0 mmol) in 5 mL of DCM was added acid chloride (**2**, 1.0 mmol) dropwise at 10 °C. After completion of the addition the reaction mixture was allowed to stir at room temperature for 3–10 h. The reaction mixture was quenched with water, neutralised by dil. HCl, extracted with CH_2Cl_2 (2 × 8 mL) and washed with brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–hexane = 2 : 8) to afford pure 2,3-dihydro-4*H*-pyran-4-ones **3**.

Ethyl 2,2-dimethyl-4-oxo-6-phenyl-2,3-dihydro-4*H*-pyran-5-carboxylate (3aa)

The reaction was carried out according to general method A using ethyl benzoylacetate (**1a**, 192 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 6 h gave **3aa** (219 mg, 80%) as a colorless crystal. M.p. 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.51 (m, 2H), 7.49–7.45 (m, 1H), 7.40–7.37 (m, 2H), 4.05 (q, J = 7.2 Hz, 2H), 2.64 (s, 2H), 1.56 (s, 6H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 170.7, 165.9, 133.9, 131.5, 128.3, 128.2, 111.4, 81.9, 61.0, 47.0, 26.1, 13.7 ppm; MS (ESI): *m*/*z* 274.1 $(M)^+$. Anal. calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.20; H, 6.65%.

Ethyl 2,2-dimethyl-6-(4-methylphenyl)-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3ba)

The reaction was carried out according to general method A using ethyl 3-(4-methylphenyl)-3-oxopropanoate (**1b**, 206 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 5 h gave **3ba** (236 mg, 82%) as a yellow solid. M.p. 88–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 4.07 (q, J = 7.0 Hz, 2H), 2.62 (s, 2H), 2.36 (s, 3H), 1.54 (s, 6H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.9, 169.7, 165.2, 141.2, 129.9, 128.0, 127.2, 109.9, 80.5, 60.0, 45.9, 25.0, 20.5, 12.7; HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{21}O_4$, 289.1440; found, 289.1461.

Ethyl 2,2-dimethyl-6-(4-methoxyphenyl)-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3ca)

The reaction was carried out according to general method A using ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (**1c**, 222 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 5 h gave **3ca** (258 mg, 85%) as a yellow solid. M.p. 66–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.12 (q, J = 7.0 Hz, 2H), 3.85 (s, 3H), 2.64 (s, 2H), 1.56 (s, 6H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 170.3, 166.5, 162.4, 130.2, 125.9, 113.7, 110.4, 81.3, 61.1, 55.4, 47.0, 26.1, 13.8 ppm; HRMS (ESI): $[M + Na]^+$ calcd for $C_{17}H_{20}NaO_5$, 327.1208; found, 327.1238.

Ethyl 2,2-dimethyl-4-oxo-6-(3,4,5-trimethoxyphenyl)-2,3-dihydro-4*H*-pyran-5-carboxylate (3da)

The reaction was carried out according to general method A using ethyl 3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**1d**, 282 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 5 h gave **3da** (309 mg, 85%) as a white solid. M.p. 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 6H), 2.63 (s, 2H), 1.56 (s, 6H), 1.06 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 169.8, 166.3, 153.1, 141.1, 128.9, 111.3, 105.7, 81.8, 61.2, 60.9, 56.2, 46.9, 26.1, 13.8 ppm; HRMS (ESI): $[M + Na]^+$ calcd for $C_{19}H_{24}NaO_7$, 387.1420; found, 387.1453.

Ethyl 6-(4-chlorophenyl)-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3ea)

The reaction was carried out according to general method A using ethyl 3-(4-chlorophenyl)-3-oxopropanoate (**1e**, 226 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 3 h gave **3ea** (277 mg, 90%) as a white solid. M.p. 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 4.09 (q, J = 7.0 Hz, 2H), 2.65 (s, 2H), 1.56 (s, 6H), 1.06 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 169.1, 165.8, 137.8, 132.2, 129.6, 128.7, 111.6, 82.1, 61.2, 47.0, 26.1, 13.7 ppm; HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{18}ClO_4$, 309.0894; found, 309.0921.

Ethyl 6-(2-chlorophenyl)-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3fa)

The reaction was carried out according to general method A using ethyl 3-(2-chlorophenyl)-3-oxopropanoate (**1f**, 226 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 7 h **3fa** (246 mg, 80%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.31 (m, 1H), 7.29–7.24 (m, 1H), 7.21–7.19 (m, 1H), 7.18–7.15 (m, 1H), 3.84 (q, J = 7.2 Hz, 2H), 2.58 (s, 2H), 1.47 (s, 6H), 0.75 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.4, 171.2, 164.2, 133.8, 132.6, 131.3, 129.8, 129.5, 126.5, 112.5, 83.3, 60.6, 47.5, 26.1, 13.5 ppm. HRMS (ESI): $[M + H]^+$ calcd for $C_{16}H_{18}ClO_4$, 309.0894; found, 309.0895.

Ethyl 2,3-dimethyl-4-oxo-6-phenyl-2,3-dihydro-4*H*-pyran-5-carboxylate (*tc*-3ab)

The reaction was carried out according to general method A using ethyl benzoylacetate (**1a**, 192 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), tigloyl chloride (**2b**, 110 μL, 1.0 mmol) in DCM (4 mL). Condition: room temperature, 7 h. The crude diastereomeric mixture was purified through a silica gel column chromatography (hexane–EtOAc = 8 : 2). First eluted was compound *trans*-**3ab** (128 mg, 47%), obtained as a colourless solid and second eluted was *cis*-**3ab** (86 mg, 31%), obtained as pale yellow paste. The overall yield of *tc*-**3ab** was 78% (214 mg). Compound *trans*-**3ab**: M.p. 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.56 (m, 2H), 7.50–7.46 (m, 1H),

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7.41–7.37 (m, 2H), 4.44–4.36 (m, 1H), 4.13–4.04 (m, 2H), 2.52–2.43 (m, 1H), 1.56 (d, J = 6.0 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 171.4, 166.2, 133.2, 131.7, 128.4, 128.3, 111.8, 80.9, 61.2, 44.5, 19.1, 13.7, 10.0 ppm; MS (ESI): m/z 274.1 $(M)^+$. Anal. calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.18; H, 6.64%. Compound *cis*-**3ab**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.55 (m, 2H), 7.50–7.46 (m, 1H), 7.41–7.37 (m, 2H), 4.83–4.78 (m, 1H), 4.12–4.02 (m, 2H), 2.56–2.50 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.16 (d, J = 7.2 Hz, 3H), 0.99 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.2, 171.7, 166.1, 133.2, 131.8, 128.4, 128.3, 110.9, 78.5, 61.1, 43.4, 15.7, 13.7, 8.9 ppm; MS (ESI): m/z 274.0 $(M)^+$. Anal. calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.22; H, 6.67%.

Ethyl 2-dimethyl-4-oxo-6-phenyl-2,3-dihydro-4*H*-pyran-5-carboxylate (3ac)

The reaction was carried out according to general method A using ethyl benzoylacetate (**1a**, 192 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), crotonoyl chloride (**2c**, 96 μL, 1.0 mmol) in DCM (4 mL) for 7 h gave **3ac** (182 mg, 70%) as a colorless solid. M.p. 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.57 (m, 2H), 7.52–7.47 (m, 1H), 7.43–7.38 (m, 2H), 4.83–4.74 (m, 1H), 4.13–4.03 (m, 2H), 2.67–2.55 (m, 2H), 1.58 (d, J = 6.4 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 172.4, 165.9, 133.2, 131.7, 128.4, 128.3, 112.4, 76.2, 61.1, 42.4, 20.3, 13.7 ppm; MS (ESI): m/z 261.3 $(M + 1)^+$. Anal. calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.40; H, 6.26%.

Ethyl 2,2-dimethyl-4-oxo-6-(thiophen-2-yl)-2,3-dihydro-4*H*-pyran-5-carboxylate (3ga)

The reaction was carried out according to general method A using ethyl 3-oxo-3-(thiophen-2-yl)propanoate (**1g**, 198 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 6 h gave **3ga** (246 mg, 88%) as a pale yellow color crystal. M.p. 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 4.8 Hz, 1H), 7.44–7.43 (m, 1H), 7.05–7.02 (dd, J = 4.8, 4.0 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 2.57 (s, 2H), 1.49 (s, 6H), 1.19 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 166.2, 161.5, 135.3, 131.7, 131.0, 128.0, 109.9, 81.8, 61.6, 46.9, 26.0, 13.9; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{17}O_4S$, 281.0848; found, 281.0869. Single crystals suitable for X-ray studies were grown from a solution of **3ga** in hexane–ethyl acetate (3 : 7).

Ethyl 6-(furan-2-yl)-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3ha)

The reaction was carried out according to general method A using ethyl 3-(furan-2-yl)-3-oxopropanoate (**1h**, 182 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 7 h gave **3ha** (227 mg, 86%) as a yellow solid. M.p. 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.52 (dd, J = 1.6, 0.8 Hz, 1H), 6.98–6.97 (dd, J = 3.6, 0.4 Hz, 1H), 6.52–6.51 (dd, J = 3.4, 1.8 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 2.61 (s, 2H), 1.52 (s, 6H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 165.5, 156.8, 146.9, 146.1, 116.1, 112.3, 109.2, 81.6, 61.4, 47.1, 26.1, 14.1; HRMS (ESI): $[M + H]^+$ calcd for $C_{14}H_{17}O_5$, 265.1076; found, 265.1097.

Ethyl 2,2,6-trimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3ja)

The reaction was carried out according to general method A using ethyl acetoacetate (**1j**, 130 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 7 h gave **3ja** (159 mg, 75%) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24 (q, J = 7.0 Hz, 2H), 2.49 (s, 2H), 2.16 (s, 3H), 1.41 (s, 6H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 175.4, 165.8, 110.8, 81.5, 60.9, 47.1, 26.2, 20.8, 14.2 ppm; MS (ESI): m/z 212.1 $(M)^+$. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.46; H, 7.68%.

Ethyl 2,6-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3jc)

The reaction was carried out according to general method A using ethyl acetoacetate (**1j**, 130 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), crotonoyl chloride (**2c**, 96 μL, 1.0 mmol) in DCM (4 mL) for 8 h gave **3jc** (119 mg, 60%) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61–4.48 (m, 1H), 4.27 (q, J = 7.0 Hz, 2H), 2.48–2.46 (m, 2H), 2.19 (s, 3H), 1.46 (d, J = 6.4 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1, 176.7, 165.5, 112.4, 75.6, 60.9, 42.3, 20.2, 20.1, 14.1 ppm; MS (ESI): m/z 198.1 $(M)^+$. Anal. calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.78; H, 7.18%.

Methyl 6-ethyl-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3ka)

The reaction was carried out according to general method A using methyl 3-oxo-pentanoate (**1k**, 130 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 6 h gave **3ka** (170 mg, 80%) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 2.52 (s, 2H), 2.47 (q, J = 7.4 Hz, 2H), 1.43 (s, 6H), 1.16 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6, 179.5, 166.3, 109.9, 81.4, 52.0, 47.0, 27.5, 26.0, 11.2; HRMS (ESI): $[M + H]^+$ calcd for $C_{11}H_{17}O_4$, 213.1127; found, 213.1140.

Methyl 6-ethyl-2,3-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (*tc*-3kb)

The reaction was carried out according general method A using methyl 3-oxo-pentanoate (**1k**, 130 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), tigloyl chloride (**2b**, 110 μL, 1.0 mmol) in DCM (4 mL). Condition: room temperature, 7 h. The crude diastereomeric mixture was purified through a silica gel column chromatography (hexane–EtOAc = 8 : 2). First eluted was compound *trans*-**3kb** (99 mg, 47%), obtained as a pale yellow liquid and second eluted was *cis*-**3kb** (66 mg, 31%), obtained as a pale yellow liquid. The overall yield of *tc*-**3kb** was 78% (165 mg). Compound *trans*-**3kb**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20–4.13 (m, 1H), 3.80 (s, 3H), 2.52–2.42 (m, 2H), 2.36–2.26 (m, 1H), 1.46 (d, J = 6.4 Hz, 3H), 1.17 (t, J = 7.4 Hz, 3H), 1.10 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 180.0, 166.5, 110.6, 80.5, 52.1, 44.4, 27.2, 19.0, 11.2, 10.3 ppm; MS (ESI): m/z 212.0 $(M)^+$. Anal.

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calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.42; H, 7.66. Compound *cis*-**3kb**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.61–4.55 (m, 1H), 3.79 (s, 3H), 2.51–2.41 (m, 3H), 1.36 (d, J = 6.4 Hz, 3H), 1.18 (t, J = 7.6 Hz, 3H), 1.07 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 180.2, 166.4, 109.9, 80.5, 52.1, 43.3, 27.1, 15.5, 11.3, 9.1 ppm; MS (ESI): m/z 212.0 $(M)^+$. Anal. calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.46, H, 7.69.

Methyl 2-ethyl-6-methyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3lf)

The reaction was carried out according to general method A using methyl acetoacetate (**1l**, 116 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), *trans*-2-pentenoyl chloride (**2f**, 114 μL, 1.0 mmol) in DCM (4 mL) for 10 h gave **3lf** (99 mg, 50%) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33–4.26 (m, 1H), 3.74 (s, 3H), 2.44–2.41 (m, 2H), 2.17 (s, 3H), 1.82–1.64 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3, 177.7, 166.1, 111.9, 80.4, 52.0, 40.3, 27.2, 20.4, 9.0 ppm; MS (ESI): m/z 198.1 $(M)^+$. Anal. calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.81; H, 7.19%.

Ethyl 6-(2-ethoxy-2-oxoethyl)-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3ma)

The reaction was carried out according to general method A using diethyl 1,3-acetonedicarboxylate (**1m**, 202 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 10 h gave **3ma** (128 mg, 45%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.25 (q, J = 7.0 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.57 (s, 2H), 2.57 (s, 2H), 1.46 (s, 6H), 1.32–1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3, 171.7, 167.6, 164.9, 111.2, 82.6, 61.4, 61.1, 47.4, 40.5, 25.9, 14.1, 14.0 ppm; MS (ESI): m/z 284 $(M)^+$. Anal. calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.33; H, 7.16%.

Ethyl 6-(2-ethoxy-2-oxoethyl)-2-methyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3mc)

The reaction was carried out according to general method A using diethyl 1,3-acetonedicarboxylate (**1m**, 202 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), crotonoyl chloride (**2c**, 96 μL, 1.0 mmol) in DCM (4 mL) for 10 h gave **3mc** (81 mg, 30%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69–4.62 (m, 1H), 4.25 (q, J = 7.0 Hz, 2H), 4.18 (q, J = 7.0 Hz, 2H), 3.66–3.52 (m, 2H), 2.54–2.52 (m, 2H), 1.47 (d, J = 6.4 Hz, 3H), 1.31–1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3, 173.1, 167.5, 164.8, 112.8, 76.4, 61.6, 61.2, 42.6, 40.2, 20.0, 14.1, 14.0 ppm; MS (ESI): m/z 270 $(M)^+$. Anal. calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 58.06; H, 6.82%.

Ethyl 6-benzyl-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3na)

The reaction was carried out according to general method A using ethyl 3-oxo-4-phenylbutanoate (**1n**, 206 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 6 h gave **3na** (225 mg, 78%) as pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.24 (m, 5H), 4.29 (q, J = 7.2 Hz, 2H), 3.78 (s, 2H), 2.52 (s, 2H), 1.33 (s, 6H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 174.8, 165.7, 135.5, 129.0, 128.5, 127.0, 111.5, 81.6, 61.2, 47.2, 39.6, 25.9, 14.2 ppm; HRMS (ESI): $[M + H]^+$ calcd for $C_{17}H_{21}O_4$, 289.1440; found, 289.1460.

Ethyl 6-benzyl-2-methyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (3nc)

The reaction was carried out according to general method A using ethyl 3-oxo-4-phenylbutanoate (**1n**, 206 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), crotonoyl chloride (**2c**, 96 μL, 1.0 mmol) in DCM (4 mL) for 10 h gave **3nc** (192 mg, 70%) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.27 (m, 5H), 4.56–4.47 (m, 1H), 4.29 (q, J = 7.0 Hz, 2H), 3.84–3.73 (m, 2H), 2.48 (d, J = 8.0 Hz, 2H), 1.41 (d, J = 6.4 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 176.5, 165.6, 135.4, 129.0, 128.6, 127.1, 112.9, 75.9, 61.3, 42.4, 39.4, 20.1, 14.2 ppm; MS (ESI): m/z 275.3 $(M + 1)^+$. Anal. calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.29; H, 6.67%.

General method B: typical experimental procedure for the O-acylation of cyclic active methylene compounds (5)

To a suspension of cyclic active methylene compounds (**4**, 1.0 mmol), $CaCl_2$ (0.1 mmol) and Et_3N (2.0 mmol) in 4 mL of DCM was added senecioyl chloride (**2a**, 1.0 mmol) dropwise at 10 °C. After completion of the addition the reaction mixture was allowed to stir at room temperature for 3–6 h. The reaction mixture was quenched with water, neutralised by dil. HCl, extracted with CH_2Cl_2 (2 × 8 mL) and washed with brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane–EtOAc = 9 : 1) to afford pure O-acylated product **5a-b**.

2-Oxo-2*H*-chromen-4-yl 3-methylbut-2-enoate (5a)

The reaction was carried out according to general method B using 4-hydroxy-2*H*-chromen-2-one (**4a**, 162 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**,112 μL, 1.0 mmol) in DCM (4 mL) for 3 h gave **5a** (232 mg, 95%) as a white solid. M.p. 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dd, J = 8.0, 1.2 Hz, 1H), 7.59–7.55 (m, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.29 (t, J = 8.4 Hz, 1H), 6.53 (s, 1H), 6.01–6.00 (m, 1H), 2.28 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 161.8, 161.7, 158.7, 153.7, 132.6, 124.2, 122.9, 116.9, 115.9, 113.7, 104.8, 27.9, 20.9 ppm; MS (ESI): m/z 244.1 $(M)^+$. Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.97; H, 4.99%.

3-Methyl-1-phenyl-1*H*-pyrazol-5-yl 3-methylbut-2-enoate (5b)

The reaction was carried out according to general method B using 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**4b**, 174 mg, 1.0 mmol), $CaCl_2$ (11 mg, 0.1 mmol), Et_3N (278 μL, 2.0 mmol), senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in DCM (4 mL) for 6 h gave **5b** (218 mg, 85%) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.0 Hz, 2H), 7.41 (t, J = 8.0 Hz, 2H),

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7.27 (t, J = 7.4 Hz, 1H), 6.11 (s, 1H), 5.80 (s, 1H), 2.32 (s, 3H), 2.18 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 161.3, 148.9, 144.7, 138.3, 128.9, 126.8, 122.9, 113.7, 95.8, 27.7, 20.7, 14.5 ppm; MS (ESI): m/z 256.0 $(M)^+$. Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.38; H, 6.33; N, 11.06%.

3,5-Dimethoxyphenylacetic acid (8)

3,5-Dimethoxyphenylacetic acid (**8**) was prepared from 3,5-dimethoxtacetophenone (**7**) according to the literature procedure.[24] Spectral data and melting points are matched with literature procedure. M.p. 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (d, J = 2.0 Hz, 2H), 6.38 (t, J = 2.2 Hz, 1H), 3.77 (s, 6H), 3.57 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 160.9, 135.3, 107.5, 99.4, 55.3, 41.3 ppm.

Ethyl 4-(3,5-dimethoxyphenyl)-3-oxobutanoate (9)

To 3,5-dimethoxyphenylacetic acid (**8**, 196 mg, 1.0 mmol) in DCM solution at 25 °C Meldrum's acid (144 mg, 1.0 mmol), DCC (227 mg, 1.1 mmol) and DMAP (134 mg, 1.1 mmol) were added, and the solution was stirred at 25 °C for 10 h. The insoluble DCC by-product was then filtered off and the remaining solution was concentrated. The crude extract was then dissolved in EtOH (5 mL) and refluxed for 8 h. Following concentration *in vacuo*, the crude material was purified by column chromatography (hexane–EtOAc = 9 : 1) to yield the pure product **9** (133 mg, 50%) as colorless liquid. 9 : 1 keto–enol mixture was identified by ^{1}H NMR. ^{1}H NMR keto tautomer (400 MHz, $CDCl_3$): δ 6.37 (t, J = 2.4 Hz, 1H), 6.35 (d, J = 2.0 Hz, 2H), 4.17 (q, J = 7.0 Hz, 2H), 3.77 (s, 6H), 3.74 (s, 2H), 3.44 (s, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR keto tautomer (100 MHz, $CDCl_3$): δ 200.4, 167.1, 161.1, 161.0, 135.3, 107.6, 99.4, 61.4, 55.3, 50.3, 48.0, 14.1 ppm; MS (ESI): m/z 267.3 $(M + 1)^+$. Anal. calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.34; H, 6.88%.

Ethyl 6-(3,5-dimethoxybenzyl)-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (10a)

To ethyl 4-(3,5-dimethoxyphenyl)-3-oxobutanoate (**9**, 266 mg, 1.0 mmol) in dry toluene (5 mL) solution $Mg(OEt)_2$ (114 mmol, 1.0 mmol) was added and refluxed for 30 min under N_2 atm. Then senecioyl chloride (**2a**, 112 μL, 1.0 mmol) in dry ACN (1 mL) was added dropwise at 10 °C. After completion of the addition the reaction mixture was allowed to stir at room temperature for 10 h. The reaction mixture was quenched with water, neutralised by dil. HCl, extracted with EtOAc (2 × 8 mL) and washed with brine. The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography (hexane–EtOAc = 8 : 2) to afford pure **10a** (261 mg, 75%) as pale yellow solid. M.p. 40–42 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (d, J = 2.4 Hz, 2H), 6.34 (t, J = 2.2 Hz, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.76 (s, 6H), 3.70 (s, 2H), 2.52 (s, 2H), 1.35 (s, 6H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 174.4, 165.7, 160.8, 137.6, 111.6, 107.2, 99.1, 81.6, 61.2, 55.3, 47.2, 39.7, 26.0, 14.2 ppm; MS (ESI): m/z 347.3 $(M - 1)^+$. Anal. calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.66; H, 6.98%.

In the same manner, 5-carboalkoxy-2,3-dihydro-4*H*-pyranones *tc*-**10b** (*trans*-**10b** and *cis*-**10b**) and **10c** were synthesized.

Ethyl 6-(3,5-dimethoxybenzyl)-2,3-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (*tc*-10b)

The reaction was carried out similar to compound **10a** using ethyl 4-(3,5-dimethoxyphenyl)-3-oxobutanoate (9, 266 mg, 1.0 mmol), $Mg(OEt)_2$ (114 mg, 1.0 mmol) in dry toluene (5 mL) and tigloyl chloride (**2b**, 110 μL, 1.0 mmol) in ACN (1 mL) for 10 h. The crude diastereomeric mixture was purified through a silica gel column chromatography (hexane–EtOAc = 8 : 2). First eluted was compound *trans*-**10b** (146 mg, 42%), obtained as a pale yellow paste and second eluted was *cis*-**10b** (98 mg, 28%), obtained as a pale yellow paste. The overall yield of *tc*-**10b** was 70% (244 mg). Compound *trans*-**10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.38 (d, J = 2.4 Hz, 2H), 6.30–6.27 (m, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.11–4.04 (m, 1H), 3.71 (s, 2H), 3.70 (s, 6H), 2.31–2.23 (m, 1H), 1.35 (d, J = 6.4 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 175.1, 165.8, 160.9, 137.6, 112.3, 107.2, 99.1, 80.7, 61.2, 55.3, 44.6, 39.4, 19.0, 14.2, 10.2 ppm; MS (ESI): m/z 347.3 $(M - 1)^+$. Anal. calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.68; H, 6.99%. Compound *cis*-**10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (d, J = 2.0 Hz, 2H), 6.34 (s, 1H), 4.59–4.53 (m, 1H), 4.28 (q, J = 7.0 Hz, 2H), 3.76 (s, 6H), 3.70 (d, J = 4.0 Hz, 2H), 2.48–2.42 (m, 1H), 1.32–1.24 (m, 6H), 1.04 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.7, 174.2, 164.8, 159.8, 136.6, 110.6, 106.0, 98.1, 77.3, 60.2, 54.3, 42.3, 38.4, 14.3, 13.2, 8.0 ppm; MS (ESI): m/z 347.4 $(M - 1)^+$. Anal. calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.72; H, 7.02%.

Ethyl 6-(3,5-dimethoxybenzyl)-2-methyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (10c)

The reaction was carried out similar to compound **10a** using ethyl 4-(3,5-dimethoxyphenyl)-3-oxobutanoate (**9**, 266 mg, 1.0 mmol), $Mg(OEt)_2$ (114 mg, 1.0 mmol) in dry toluene (5 mL) and crotonoyl chloride (**2c**, 96 μL, 1.0 mmol) in ACN (1 mL) for 10 h. The title compounds **10c** (210 mg, 63%) was obtained as pale yellow paste after passing through a silica gel column chromatography (hexane–EtOAc = 8 : 2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (d, J = 2.4 Hz, 2H), 6.37 (t, J = 2.2 Hz, 1H), 4.58–4.49 (m, 1H), 4.3 (q, J = 7.2 Hz, 2H), 3.78 (s, 8H), 2.50–2.48 (m, 2H), 1.43 (d, J = 6.4 Hz, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 176.2, 165.6, 160.8, 137.5, 113.0, 107.2, 99.0, 75.9, 61.3, 55.3, 42.4, 39.5, 20.1, 14.2 ppm; MS (ESI): m/z 333.4 $(M - 1)^+$. Anal. calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.83; H, 6.69%.

5-Hydroxy-6,8-dimethoxy-2,2-dimethyl-4*H*-2,3-dihydronaphtho[2,3-*b*]-pyran-4-one (11a)

To ethyl 6-(3,5-dimethoxybenzyl)-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (**10a**, 348 mg, 1.0 mmol) in PPA (2.0 mL) mixture was heated at 80 °C for 15 min. The reaction mixture was quenched by crushed ice and extracted with

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EtOAc (3 × 10 mL). Finally organic layer was neutralised by 10% $NaHCO_3$ solution and EtOAc layer separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (hexane–EtOAc = 9 : 1) to afford pure **11a** (287 mg, 95%) as yellow colour solid. M.p. 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.36 (s, 1H), 6.47 (s, 1H), 6.42 (d, J = 2.0 Hz, 1H), 6.27 (d, J = 2.0 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 2.76 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 164.9, 162.4, 161.4, 154.8, 143.6, 107.0, 103.3, 102.2, 98.3, 96.4, 77.8, 56.0, 55.4, 48.3, 26.9 ppm; MS (ESI): m/z 303.1 $(M + 1)^+$. Anal. calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.62; H, 6.05%.

In the same manner, dihydronaphthopyran-4-ones *tc*-**11b** (*trans*-**11b** and *cis*-**11b**), **11c**, **11na**, **11na′**, **11nc** and **11nc′** were synthesized.

5-Hydroxy-6,8-dimethoxy-2,3-dimethyl-4*H*-2,3-dihydronaphtho[2,3-*b*]-pyran-4-one (*tc*-11b)

The reaction was carried out similar to compound **11a** using ethyl 6-(3,5-dimethoxybenzyl)-2,3-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (*tc*-**10b**, 348 mg, 1.0 mmol) in PPA (2.0 mL) for 15 min. The crude diastereomeric mixture was purified through a silica gel column chromatography (hexane–EtOAc = 9 : 1). First eluted was compound *trans*-**11b** (168 mg, 56%), obtained as a yellow solid and second eluted was *cis*-**11b** (112 mg, 37%), obtained as a yellow solid. The overall yield of *tc*-**11b** was 93% (280 mg). Compound *trans*-**11b**: M.p. 168–170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.47 (s, 1H), 6.48 (s, 1H), 6.43 (s, 1H), 6.28 (s, 1H), 4.23–4.16 (m, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.69–2.61 (m, 1H), 1.50 (d, J = 6.0 Hz, 3H), 1.26 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 165.1, 162.3, 161.3, 156.0, 143.3, 107.2, 103.0, 101.2, 98.3, 96.4, 78.0, 56.0, 55.4, 46.5, 19.8, 10.5 ppm. MS (ESI): m/z 303.1 $(M + 1)^+$. Anal. calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.69; H, 6.06%. Compound *cis*-**11b**: M.p. 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.40 (s, 1H), 6.50 (s, 1H), 6.44 (d, J = 2.0 Hz, 1H), 6.28 (d, J = 1.6 Hz, 3H), 4.61–4.55 (m, 1H), 3.96 (s, 3H), 3.88 (s, 3H), 2.72–2.65 (m, 1H), 1.39 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 165.5, 162.4, 161.4, 155.8, 143.3, 107.3, 102.5, 101.3, 98.3, 96.5, 75.3, 56.0, 55.4, 44.9, 16.5, 9.6 ppm; MS (ESI): m/z 303.0 $(M + 1)^+$. Anal. calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.75; H, 6.10%.

5-Hydroxy-6,8-dimethoxy-2-methyl-4*H*-2,3-dihydronaphtho[2,3-*b*]-pyran-4-one (11c)

The reaction was carried out similar to compound **11a** using ethyl 6-(3,5-dimethoxybenzyl)-2-methyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (**10c**, 334 mg, 1.0 mmol) in PPA (2.0 mL) for 15 min gave **11c** (259 mg, 90%) as yellow colour solid. M.p. 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.40 (s, 1H), 6.50 (s, 1H), 6.44 (d, J = 2.0 Hz, 1H), 6.28 (d, J = 2.4 Hz, 1H), 4.56–4.49 (m, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 2.81–2.67 (m, 2H), 1.50 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 165.2, 162.5, 161.4, 156.3, 143.4, 107.2, 103.7, 101.5, 101.4, 98.4, 96.5, 73.1, 56.0, 55.4, 55.3, 43.9, 21.0 ppm; MS (ESI): m/z 289.0 $(M + 1)^+$. Anal. calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.82; H, 5.64%.

5-Hydroxy-2,2-dimethyl-4*H*-2,3-dihydronaphtho[2,3-*b*]-pyran-4-one (11na) and 4-hydroxy-2,2-dimethyl-2*H*-benzo[*g*]chromen-5(3*H*)-one (11na′)

The reaction was carried out similar to compound **11a** using ethyl 6-benzyl-2,2-dimethyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (**3na**, 288 mg, 1.0 mmol) in PPA (2.0 mL) at 80 °C for 45 min. The crude mixture was purified through a silica gel column chromatography (hexane–EtOAc = 9 : 1). First eluted was compound **11na** (121 mg, 50%), obtained as a yellow solid and second eluted was **11na′** (109 mg, 45%), obtained as a yellow solid. Compound **11na**: M.p. 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.35 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.53–7.46 (m, 2H), 7.30–7.26 (m, 1H), 6.66 (s, 1H), 2.78 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 162.4, 153.6, 139.0, 130.8, 126.5, 124.4, 123.5, 120.3, 104.4, 102.7, 77.9, 48.6, 27.0 ppm; MS (ESI): m/z 240.7 $(M - 1)^+$. Anal. calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.44; H, 5.85%. Compound **11na′**: M.p. 70–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.12 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.56–7.48 (m, 2H), 7.28–7.24 (m, 1H), 6.72 (s, 1H), 2.86 (s, 2H), 1.59 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 159.4, 155.6, 139.4, 130.7, 126.4, 123.9, 123.1, 119.5, 105.3, 102.6, 80.4, 47.9, 26.5 ppm; MS (ESI): m/z 240.7 $(M - 1)^+$. Anal. calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.53; H, 5.88%.

5-Hydroxy-2-methyl-4*H*-2,3-dihydronaphtho[2,3-*b*]-pyran-4-one (11nc) and 4-hydroxy-2-methyl-2*H*-benzo[*g*]chromen-5(3*H*)-one (11nc′)

The reaction was carried out similar to compound **11a** using ethyl 6-benzyl-2-methyl-4-oxo-2,3-dihydro-4*H*-pyran-5-carboxylate (**3nc**, 274 mg, 1.0 mmol) in PPA (2.0 mL) at 80 °C for 45 min. The crude mixture was purified through a silica gel column chromatography (hexane–EtOAc = 9 : 1). First eluted was compound **11nc** (103 mg, 45%), obtained as a yellow solid and second eluted was **11nc′** (91 mg, 40%), obtained as a yellow solid. Compound **11nc**: M.p. 74–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.39 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.58–7.50 (m, 2H), 7.32 (t, J = 7.4 Hz, 1H), 6.72 (s, 1H), 4.61–4.53 (m, 1H), 2.84–2.74 (m, 2H), 1.53 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 162.7, 155.1, 138.8, 130.9, 126.6, 124.4, 123.6, 120.4, 104.8, 102.0, 73.3, 44.3, 21.0 ppm. MS (ESI): m/z 226.7 $(M - 1)^+$. Anal. calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.79; H, 5.35%. Compound **11nc′**: M.p. 66–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.13 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.57–7.49 (m, 2H), 7.29–7.26 (m, 1H), 6.75 (s, 1H), 4.83–4.77 (m, 1H), 2.91–2.75 (m, 2H), 1.67 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.0, 161.1, 155.8, 139.2, 130.7, 126.4, 123.8, 123.2, 118.9, 106.1, 103.1, 75.1, 43.5, 20.7 ppm. MS (ESI): m/z 226.7 $(M - 1)^+$. Anal. calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.83; H, 5.39%.

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