

Annulation of 2*H*-Pyran onto 1-Oxa- or 1-Azacyclohexane-2,4-diones and Their Analogues via Sequential Condensation with α-Substituted Enals and 6π-Electrocyclization

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2*H*-Pyrans are constructed on a 1-oxa- or 1-azacyclohexane-2,4-dione core via Knoevenagel condensation with enals followed by 6π-electrocyclization, which are readily catalyzed with ethylenediammonium diacetate. This formal [3 + 3] strategy constitutes C–O and C–C bond making and the diastereomer formation is circumvented using 6,6-disubstitution with the same aryl group in the 1-oxacyclohexane-2,4-diones. This facile methodology significantly advances the access to polysubstituted bicyclic 2*H*-pyrans with a versatile substrate choice and improved stability of the product.

Pyran rings including dihydro and tetrahydro analogues are widely found as key structural motifs in various natural products, and their biological significance has accordingly stimulated synthetic activities.[1] Among the known protocols for the synthesis of 2*H*-pyran[2] the electrocyclization of 2,4-diene-2-ones is a highly straightforward method in terms of easy C–O bond formations under thermal conditions, availability of the starting materials with many choices of substituents, and versatility of the resulting oxa-2,4-cyclohexenes for further transformations.[3] The iminium conditions are usually employed for the preparation of 2,4-diene-2-one intermediates by the reaction of 1,3-dicarbonyls with the conjugated 2-alkenals.[4] However, this iminium-based strategy for the synthesis of 2*H*-pyrans has only been successful using 1,3-dicarbonyls of highly enolizable structures, such as cyclohexane-1,3-diones,[5] 4-hydroxycoumarin,[6] 4-hydroxypyrones,[7] and others[8] as the reactant. In addition to the iminium activation, acid-catalyzed protocols with Lewis acids, such as $InCl_3$,[9] $BF_3 \cdot Et_2O$, $TiCl_4$, $In(OTf)_3$,[10] Brønsted acids,[10] and I_2[11] have been developed to dictate the synthesis of the same 2*H*-pyran structures.

We previously reported the synthesis of 2,3,6-trisubstituted 2*H*-pyran-5-carboxylates from 2-substituted enals and acyclic 3-oxoalkanonates, in which we discussed the role of the C2 substituent of enals for the favorable formation of 2*H*-pyrans.[12] Thus, the enals without an α-substituent led to the ensuing Michael addition to the initially formed 2,4-diene-2-ones, rather than electrocyclization.[13] In the meantime, we found that the obtained 2,3,6-trisubstituted 2*H*-pyran-5-carboxylates were unstable during storage, and furthermore this protocol cannot be applied to the reaction of 3-oxoalkanamides. Therefore, it is worth addressing the following unsolved issues, i.e., whether the substituent effect would arise in the sequential condensation of the cyclic structures of the keto ester, feasibility on keto amides, and stability of the resulting bicyclic 2*H*-pyrans. In connection with our interest in developing bicyclic pyrans as a scaffold for biologically relevant compounds, like artemisinins known as antimalarial agents,[14] we examined the reactions of cyclic substrates such as the 1-oxa- or 1-azacyclohexane-2,4-diones **II** and enals **I** bearing an α-substituent R^1 and compared their reactivity to that of the acyclic 1,3-dicarbonyls. We also attempted to optimize the conditions by choosing the amine bases, solvents, and MW irradiation technique (Scheme 1).

Results and Discussion

To ensure the reaction of the cyclic β-keto ester and the iminium of α-substituted enals, we employed compounds **2**, and examined the feasibility to produce the corresponding bicyclic 2*H*-pyrans **3**. The starting keto esters **2** were prepared by the reaction of the substituted benzaldehydes **4** with the dianion from 3-oxobutanoate generated either with LDA or simply with K_2CO_3 by heating in ethanol (Scheme 2).[15]

The reactivity of **2** toward **1** was affected by the kind of amine base and solvent used. Contrary to our previous study on the reaction of acyclic β-keto esters with α-substituted enals,[12] attempts using secondary amines, such as piperidine, pyrrolidine, diisopropylamine, and proline in THP or dichloromethane, resulted in a low yield of the target compound **3**. In place of these secondary amines, we tried to use primary mono- and diamines for the iminium formation and the ensuing condensation. Especially, ethylenediammonium diacetate (EDDA) has found potential uses as a catalyst in the reaction of 1,3-dicarbonyls or their equivalents with various type of aldehydes including enals, in acetonitrile,[5] or ionic liquids,[16] or under solvent-free conditions.[8]

Various conditions were tested for the reaction of **2f** and **1f** and the results are summarized in Table 1. As shown in Entry 1, the condensation–6π-electrocyclization sequence was achieved with the 2-aminoethanol–acetic acid mixture, though

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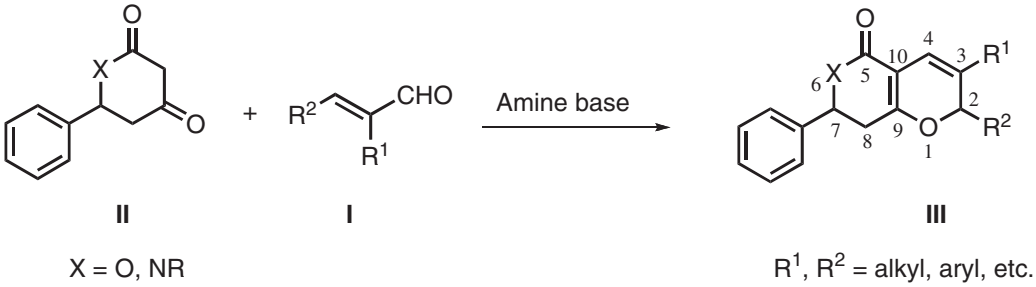
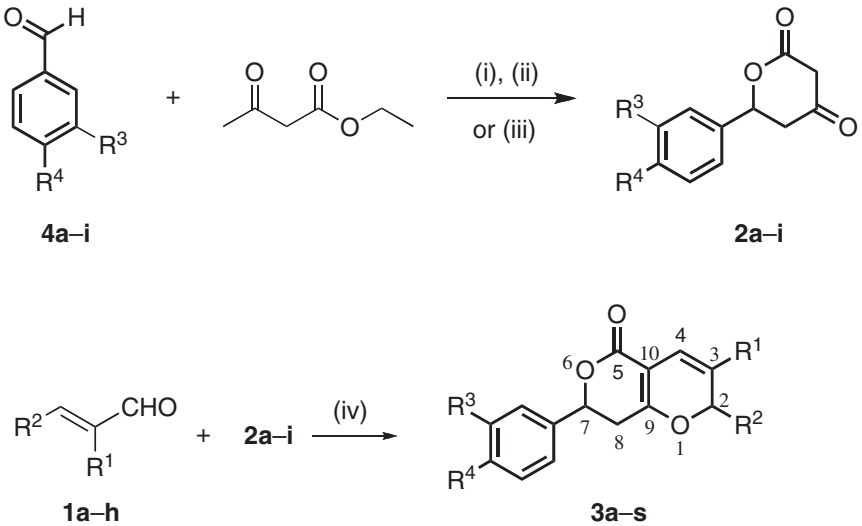


Scheme 1. Annulation of 2*H*-pyran onto 1-oxa- or 1-azacyclohexane-2,4-diones with enals, forming the 1,6-dioxa- or 6-aza-1-oxabicyclo[4.4.0]deca-3,9-dien-5-ones.



Compound **1**: $R^1 = R^2 =$ Me (**1a**); $R^1 = R^2 = -(CH_2)_4-$ (**1b**); R^1 = Me, R^2 = 4-$MeOC_6H_4$ (**1c**); R^1 = Me, R^2 = Ph (**1d**); R^1 = Me, R^2 = 4-BrC_6H_4 (**1e**); R^1 = Me, R^2 = 4-$NO_2C_6H_4$ (**1f**); R^1 = Me, R^2 = 4-$MeO_2CC_6H_4$ (**1g**); R^1 = Me, R^2 = 4-ClC_6H_4 (**1h**)
Compound **2**: R^3 = H, R^4 = Br (**2a**); R^3 = Cl, R^4 = H (**2b**); R^3 = MeO, R^4 = H (**2c**); R^3 = H, R^4 = F (**2d**); R^3 = H, $R^4 = CF_3$ (**2e**); R^3 = H, R^4 = Cl (**2f**); $R^3 = R^4$ = MeO (**2g**); R^3 = H, R^4 = MeO (**2h**); R^3 = Br, R^4 = H (**2i**)

Scheme 2. Synthesis of 1,6-dioxabicyclo[4.4.0]-3,9-diene-5-ones **3**. Reagents and conditions: (i) LDA, THF, 0 °C, 1–3 h; (ii) HCl (pH 1); (iii) K_2CO_3, EtOH, 45 °C, 16–18 h, HCl(aq); (iv) ethylenediammonium diacetate (EDDA) (5 mol %), MeOH, 2–3 h, 60 °C.

the yield of the desired **3m** is low (15%). The formation of **3m** is improved to 58% using the ethylenediamine–acetic acid mixture in THP (Entry 2). Since these yields are moderate for the desired 2*H*-pyran **3m** irrespective of the solvents, such as THP, THF, and CH_2Cl_2, at ambient temperature for 24 h, we examined the effect of a protic solvent on this reaction. To our delight, the addition of methanol to aprotic solvent CH_2Cl_2 improved the yield to 82% (Entry 5). In order to avoid the use of the unpleasant solvent CH_2Cl_2, the reaction was conducted in methanol (Entry 6), giving the desired **3m** in good yield. Finally, the desired 2*H*-pyran **3m** was obtained in 80% yield by adopting the conditions of heating at 60 °C in methanol for the short reaction period of 2 h (Entry 7). This reaction time was further decreased to a few minutes, by applying MW irradiation at 60 °C,[16] though the yield decreased to 64% (Entry 8).

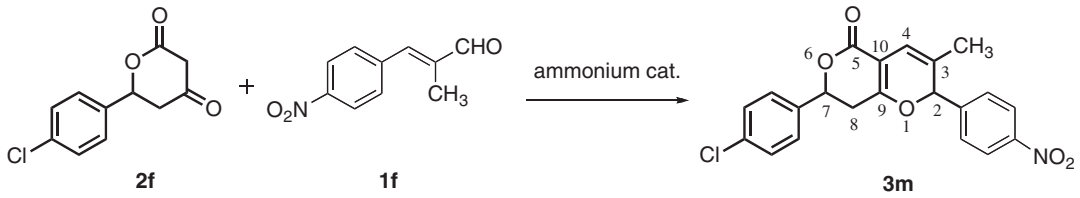
We subsequently examined the scope of the reaction using the optimized conditions (Entry 7, Table 1) for various aromatic ring-substituted cyclic keto esters **2** and α,β-unsaturated aldehydes **1**. These results are summarized in Table 2.

The effect of the kinds of substituents at the β-carbon of α,β-unsaturated aldehydes **1** on the reaction has also been studied. The optimized conditions can be effectively used for the reaction of **1** substituted with either an aliphatic or aromatic group at the β-carbon. In Table 2, Entries 1–5, the yields of **1a** having an aliphatic substituent ($R^1 = R^2 = CH_3$) are lower than that obtained with cyclic aldehydes **1b** ($R^1 = R^2 = -(CH_2)_4-$) (Entry 6). No significant effect is observed for aromatic R^2 bearing electron-withdrawing or -donating groups (Entries 7, 8, and 11–19) compared to the aromatic R^2 without such groups (Entries 9 and 10).

In spite of the smooth formation of a 2,3-disubstituted 2*H*-pyran onto the cyclic β-keto ester **2** by the condensation–6π-cyclization sequence, the limitation of this method was encountered in the reaction of **2f** with cinnamaldehyde which lacks an α-substituent. Thus, the reaction of **2f** and cinnamaldehyde under the iminium conditions described above resulted in a complicated product mixture.

Since the present condensation and cyclization sequence invoked the installation of an R^1 substituent at the C2 of the

Table 1. Optimization of the Conditions for the Reaction of **2f** and **1f** Using Ethylenediammonium Diacetate (EDDA)[a)]



2f **1f** **3m**

Entry	Ammonium cat.[b)]	Solvent (10 mL)	Temp/°C	Time/h	Yield[c),d)]/%
1	A	THP	rt.	24	15
2	B	THP	rt.	24	58
3	B	THF	rt.	24	45
4	B	CH_2Cl_2	rt.	24	40
5	B	CH_2Cl_2:MeOH = 1:1	rt.	24	82
6	B	MeOH	rt.	24	78
7	B	MeOH	60	2	80
8[e)]	B	MeOH	60	2 min	64

a) Reactions were carried out using **2f** (1.0 mmol) and **1f** (1.0 mmol) with ammonium catalyst at prescribed temperature and for indicated time. b) A: 2-Hydroxyethylammonium acetate (5 mol %), B: ethylenediammonium diacetate (EDDA, 5 mol %). c) Yields based on chromatographically isolated products. d) All products were a 1:1 mixture of diastereomers. e) A mixture of **2f** (0.5 mmol) and **1f** (0.5 mmol) in the presence of EDDA (5 mol %) was irradiated with MW at 60 °C for 2 min.

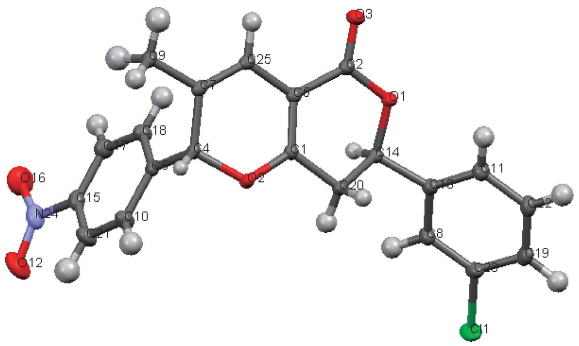


Figure 1. ORTEP drawing of crystal **3l**.

enals **1**, the reaction mechanism for formation of **3** can be rationalized as described in Scheme 3. Thus, the Knoevenagel condensation **1** and **2** would proceed via the iminium **A**, affording the 2,4-dienones **B** and **C**, the stereochemical and conformational isomers. Among them, (*E*)-**C** (s-*cis*), a requisite configuration for the ensuing electrocyclization, would be favored due to steric reasons. The equilibration between (*Z*)-**B** and (*E*)-**C** would be catalyzed by the employed amine. Finally, the s-*cis* conformer of (*E*)-**C** undergoes a spontaneous 6π-electrocyclization to form the 2*H*-pyran **3**.

To confirm the structure of the bicyclic 2*H*-pyran **3** formed by this method, one of the isomers **3l**, obtained by the reaction of **1f** and **2b**, was subjected to X-ray crystallographic analysis to determine its relative stereochemistry at C2 and C7. As depicted in Figure 1, one of the isomers of **3l**, isolated by recrystallization, was unambiguously assigned as 2,7-*trans* based on the X-ray analysis.

To our disappointment, the reactions of the 5-substituted **2a**–**2i** with 3-aryl-2-alkenals **1** were not stereoselective, providing a mixture of the 2,7-*cis*- and 2,7-*trans* isomers **3a**–**3s** in an almost 1:1 ratio, which were hard to separate by usual flash chromatography. Therefore, we tried to eliminate the stereocenter at the C6 of the δ-lactone core **2** through attachment of the same two substituents. Thus, the 6,6-disubstituted 1-oxacyclohexane-2,4-dione **6** was prepared by the reaction of dianion from 3-oxobutanoate and benzophenone (**5**) followed by an acidic workup based on the method reported (Scheme 4).[15]

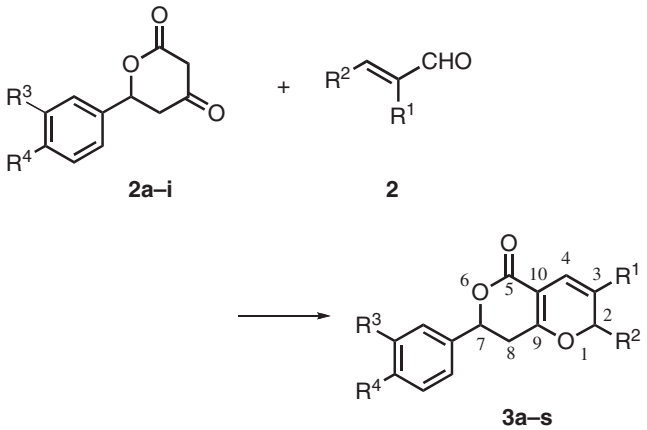
In a similar manner as described above, annulation of 2*H*-pyran onto 1-oxacyclohexane-2,4-dione **6** was achieved by the reaction with α-substituted enals **1** using ethylenediammonium diacetate as a catalyst, giving the corresponding formal [3 + 3] adducts **7a**–**7d** in good yields (Table 3). This reaction was not affected by two substituents at the C6 position of **6**.

Subsequently, we examined the annulations of the 2*H*-pyran ring onto the *N*-protected 1-azacyclohexane-2,4-diones **10** by applying the above optimized conditions. In our preceding paper,[12] we encountered difficulty in the sequential condensation and 6π-electrocyclization with acyclic β-keto amides. This was in sharp contrast to the smooth reaction using β-keto esters, which could be ascribed to the electron-releasing nature of the nitrogen atom of the amide.

The cyclic β-keto amides **10** were prepared by the Mannich reaction of benzaldehydes **4** and malonic acid which was followed by *N*-protection and the subsequent Claisen reaction with Meldrum acid based on reported methods (Scheme 5).[17]

To our delight, the condensation–6π-electrocyclization sequence on the cyclic amides **10** was achieved by the reaction with α-substituted enals **1**, affording the corresponding **11**. Thus, the cyclic β-keto amides were more reactive than the acyclic ones due to absence of intramolecular hydrogen bonding in enol form. As shown in Table 4, Entries 1–4, this reaction was not affected by the kind of substitution, electron-withdrawing or -donating nature of aromatic group at the β-carbon of **1**. Unfortunately, this reaction sequence, affording the 6-aza-1-oxabicyclo[4.4.0]deca-3,9-dien-5-ones **11**, was not stereoselective with respect to the substituents at C2 and C7.

Table 2. Scope of the Reaction with Various 6-Aryl-1-oxacyclohexane-2,4-diones **2** and α,β-Unsaturated Aldehydes **1**[a)]



Entry	Compd	R^1	R^2	R^3	R^4	Yield[b),c)] /%
1	**3a**	Me	Me	H	Br	60
2	**3b**	Me	Me	Cl	H	63
3	**3c**	Me	Me	H	F	69
4	**3d**	Me	Me	MeO	MeO	59
5	**3e**	Me	Me	H	CF_3	60
6	**3f**	–$(CH_2)_4$–		H	CF_3	80
7	**3g**	Me	4-$MeOC_6H_4$	H	Cl	76
8	**3h**	Me	4-$MeOC_6H_4$	H	CF_3	75
9	**3i**	Me	Ph	MeO	MeO	74
10	**3j**	Me	Ph	H	CF_3	70
11	**3k**	Me	4-BrC_6H_4	H	Cl	70
12	**3l**	Me	4-$NO_2C_6H_4$	Cl	H	76
13	**3m**	Me	4-$NO_2C_6H_4$	H	Cl	80
14	**3n**	Me	4-$NO_2C_6H_4$	H	MeO	73
15	**3o**	Me	4-$NO_2C_6H_4$	MeO	MeO	74
16	**3p**	Me	4-$NO_2C_6H_4$	Br	H	71
17	**3q**	Me	4-$MeO_2CC_6H_4$	H	CF_3	76
18	**3r**	Me	4-ClC_6H_4	H	CF_3	75
19	**3s**	Me	4-ClC_6H_4	H	Cl	68

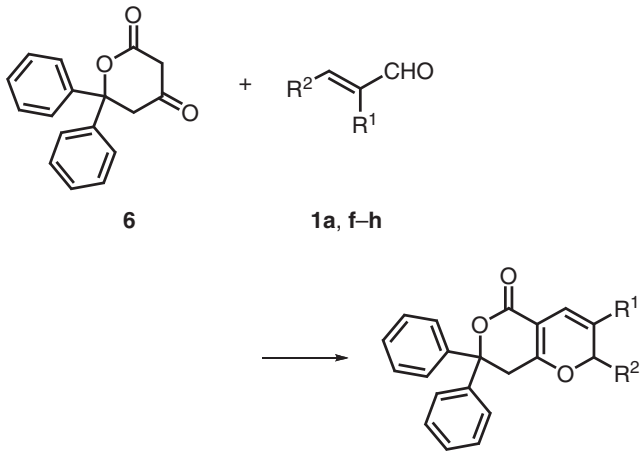
a) Carried out by the reaction of keto esters (1.0 mmol) and enals (1.0 mmol) with EDDA (5 mol %) in MeOH (10 mL) at 60 °C for 2 h. b) Isolated products. c) All products were a 1:1 mixture of diastereomers.

Finally, we verified the scope of this reaction by applying the optimized conditions to the condensation–6π-electrocyclization of the benzopyridone derivative **12** with α-substituted enals **1**. The reaction smoothly proceeded under the above conditions compared with the reported procedure that employed the enals bearing no α-substitution (Table 5).

Conclusion

We developed a convergent access to the polysubstituted 1,6-dioxa- or 6-aza-1-oxabicyclo[4.4.0]deca-3,9-dien-5-ones from 1-oxa- or 1-azacyclohexane-2,4-diones and α-substituted enals. This protocol involves the tandem Knoevenagel condensation, which was readily catalyzed with ethylenediammonium diacetate, and the subsequent 6π-electrocyclization. The feasibility was dependent on the presence of a C2 substituent on the enals. Cyclic 1,3-dicarbonyls were shown to be more

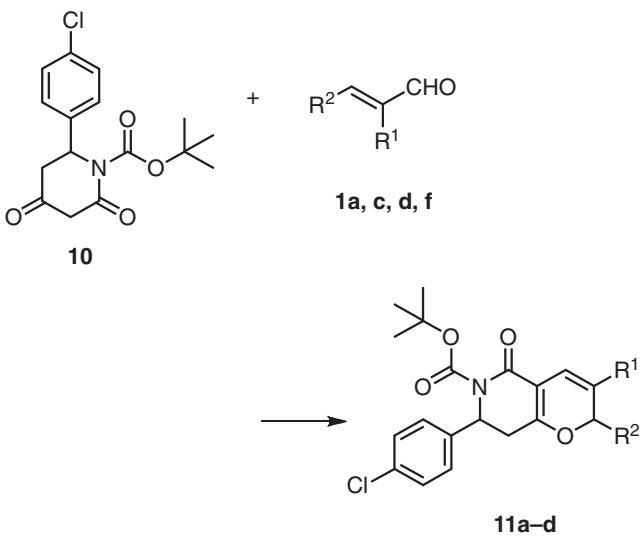
Table 3. Scope of the Reaction of **6** with Various 3-Aryl-2-methyl-2-enals **1**[a)]



Entry	Compound	R^1	R^2	Yield[b)] /%
1	**7a**	Me	4-$NO_2C_6H_4$	73
2	**7b**	Me	4-$MeOC_6H_4$	68
3	**7c**	Me	4-ClC_6H_4	75
4	**7d**	Me	4-$MeO_2CC_6H_4$	78

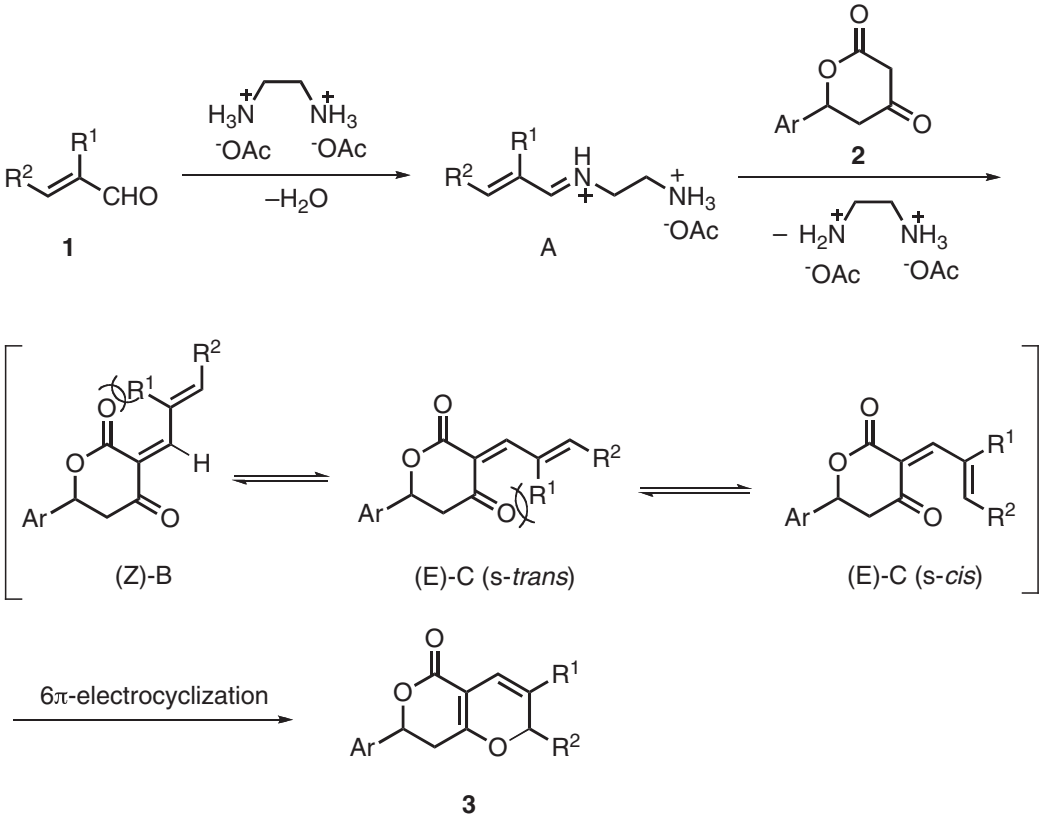
a) Carried out by the reaction of keto esters (1.0 mmol) and enals (1.0 mmol) with EDDA (5 mol %) in MeOH (10 mL) at 60 °C for 2 h. b) Isolated products.

Table 4. Scope of the Reaction of **10** with Various 3-Aryl-2-methyl-2-enals **1**[a)]

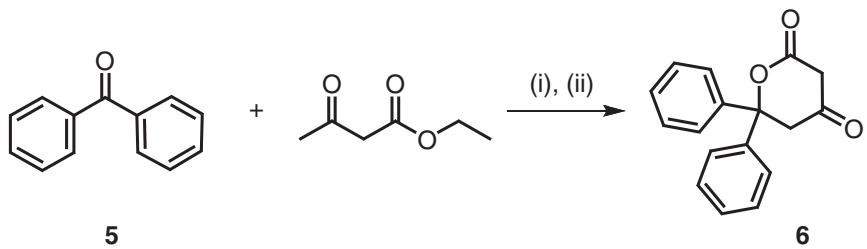


Entry	Compd	R^1	R^2	Yield[b),c)] /%
1	**11a**	Me	4-$NO_2C_6H_4$	71
2	**11b**	Me	4-$MeOC_6H_4$	69
3	**11c**	Me	Ph	62
4	**11d**	Me	Me	74

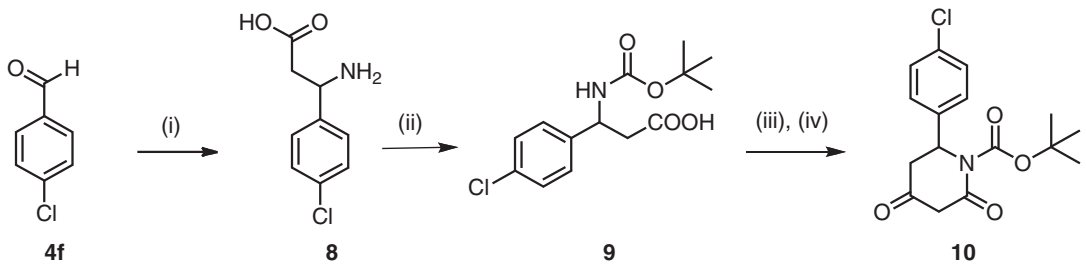
a) Carried out by the reaction of keto amides (1.0 mmol) and enals (1.0 mmol) with EDDA (5 mol %) in MeOH (10 mL) at 60 °C for 2 h. b) Isolated products. c) All products were a 1:1 mixture of diastereomers.



Scheme 3. Rationale for favorable formation of **3** by the condensation of **1** and **2** catalyzed by EDDA followed by 6π-electrocyclization.



Scheme 4. Synthesis of β-keto δ-lactone **6**. Reagents and conditions: (i) NaH, *n*-BuLi, THF, 0 °C; (ii) NaOH, THF, 0 °C.



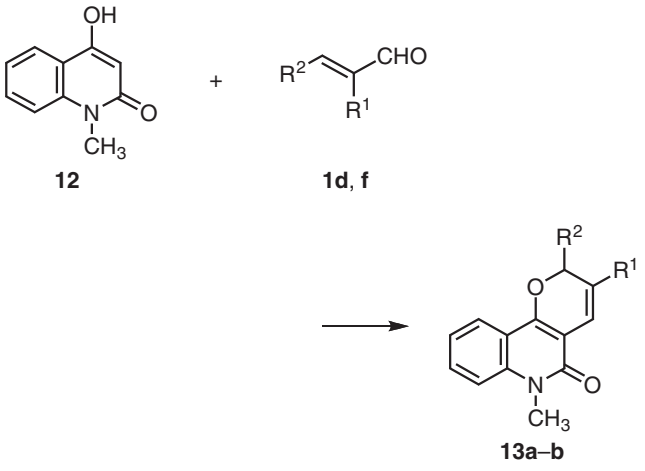
Scheme 5. Synthesis of *N*-protected β-keto amides **10**: (i) malonic acid, ammonium acetate, EtOH, reflux, 5 h; (ii) $(Boc)_2O$, dioxane/water = 10/1, rt, overnight; (iii) meldrum acid, DMAP, DCC, DCM, 40 °C, overnight; (iv) ethyl acetate, reflux, 2 h.

reactive than acyclic ones, especially in the case of the amides. Though the reaction of the C6 monosubstituted dicarbonyl substrate with enals was non-stereoselective, this issue was solved by substitution with the same group at the C6 position. The resulting 2*H*-pyrans installed in the bicyclic system were more stable than that in the monocyclic ones, and further conversion of the resulting cyclized compounds into various biologically relevant derivatives is our ongoing study.

Experimental

The commercially obtained reagents were used without further purification. The ^{1}H NMR, ^{13}C NMR spectra were

Table 5. Scope of the Reaction of **12** with Various 3-Aryl-2-methyl-2-enals **1**[a)]



Entry	Compd	R^1	R^2	Yield[b)]/%
1	**13a**	Me	4-$NO_2C_6H_6$	95
2	**13b**	Me	Ph	92

a) Carried out by the reaction of **12** (1.0 mmol) and enals (1.0 mmol) with EDDA (5 mol %) in MeOH (10 mL) at 60 °C for 2 h. b) Isolated products.

measured on the Varian INOVA-600 or Varian INOVA-400 spectrometer, using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Melting points were determined on a J-Science RFS-10 hot stage microscope. MW reaction was performed with μReactorEX, Shikoku Instrumentation Co., Ltd., operated at 2.46 GHz.

Representative Procedure for the Synthesis of 7-(4-Bromophenyl)-2,3-dimethyl-7,8-dihydropyrano[4,3-*b*]-pyran-5(2*H*)-one (3a). To a solution of (*E*)-2-methylbut-2-enal (**1a**, 84 mg, 1.0 mmol) in MeOH (10 mL), **2a** (259 mg, 1.0 mmol) and ethylenediammonium diacetate (5 mol %) were consecutively added. The reaction mixture was stirred at 60 °C for 2 h. After the reaction (checked by TLC), solvent was concentrated under reduced pressure and water was added to the residue. The crude products were extracted with ethyl acetate, dried over $MgSO_4$ and purified by flash column chromatography.

Synthesis of 7-(4-Chlorophenyl)-3-methyl-2-(4-nitrophenyl)-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3m) by Microwave (MW) Irradiation. The solution of (*E*)-2-methyl-3-(4-nitrophenyl)acrylaldehyde (**1f**, 95 mg, 0.5 mmol), **2b** (112 mg, 0.5 mmol) and ethylenediammonium diacetate (5 mol %) in MeOH (3 mL) was irradiated with MW at 60 °C for 2 min. After the reaction (checked by TLC), it was worked up as mentioned in the general method.

7-(4-Bromophenyl)-2,3-dimethyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3a): Yield 60%; white solids; mp 92–93 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3053$, 2982, 2929, 2856, 1697, 1622, 1489, 1402, 1296, 1217, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.59–7.48 (m, 2H), 7.36–7.24 (m, 2H), 6.11 (s) and 6.06 (s) (total 1H), 5.43–5.31 (m, 1H), 4.93 (d, $J = 6.5$ Hz, 1H), 2.77 (dt, $J = 17.8$, 11.8 Hz, 1H), 2.56 (ddd, $J = 17.5$, 6.7, 4.2 Hz, 1H), 1.75 (s, 2H), 1.58 (s, 1H), 1.45 (d, $J = 6.5$ Hz) and 1.36 (d, $J = 6.5$ Hz) (total 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.7, 162.5, 162.2, 137.4 (two peaks), 131.8 (two peaks), 128.1, 127.6 (two peaks), 122.5, 112.4 (two peaks), 101.52, 101.1, 77.8 (two peaks), 76.1, 75.7, 34.1, 33.9, 19.4 (two peaks), 18.8 (two peaks). Anal. Calcd for $C_{16}H_{15}BrO_3$: C, 57.33; H, 4.51%. Found: C, 57.30; H, 4.38%.

7-(3-Chlorophenyl)-2,3-dimethyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3b): Yield 63%; white solids; mp 101–102 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3052$, 2978, 2935, 2860, 1697, 1624, 1495, 1402, 1284, 1211, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, $J = 1.4$ Hz, 1H), 7.38–7.20 (m, 3H), 6.12 (s) and 6.07 (s) (total 1H), 5.38 (t, $J = 3.6$ Hz) and 5.36 (t, $J = 3.6$ Hz) (total 1H), 4.93 (dq, $J = 13.1$, 6.5 Hz, 1H), 2.78 (m, 1H), 2.58 (m, 1H), 1.75 (s, 2H), 1.59 (s, 1H), 1.45 (d, $J = 6.5$ Hz) and 1.37 (d, $J = 6.5$ Hz) (total 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.9, 164.6, 162.5, 162.1, 140.3 (two peaks), 134.6, 129.9 (two peaks), 128.7, 128.1, 127.7, 126.1, 124.0 (two peaks), 112.3 (two peaks), 101.5, 101.1, 77.8 (two peaks), 75.9, 75.5, 34.0, 33.9, 19.4 (two peaks), 18.9 (two peaks). Anal. Calcd for $C_{16}H_{15}ClO_3$: C, 66.10; H, 5.20%. Found: C, 66.28; H, 5.29%.

7-(4-Fluorophenyl)-2,3-dimethyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3c): Yield 69%; white solids; mp 84–85 °C (ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3055$, 2985, 2941, 1718, 1637, 1514, 1419, 1228, 1159, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.32 (m, 2H), 7.15–7.00 (m, 2H), 6.12 (s) and 6.07 (s) (total 1H), 5.40 (t, $J = 2.1$ Hz) and 5.37 (t, $J = 2.1$ Hz) (total 1H), 4.93 (dq, $J = 13.1$, 6.5 Hz, 1H), 2.80 (td, $J = 17.2$, 12.2 Hz, 1H), 2.55 (ddd, $J = 17.4$, 11.3, 4.1 Hz, 1H), 1.75 (s, 2H), 1.58 (s, 1H), 1.45 (d, $J = 6.5$ Hz) and 1.37 (d, $J = 6.5$ Hz) (total 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 165.2, 164.8, 163.5, 162.7, 162.3, 161.8, 134.1, 128.0, 127.8 (two peaks), 127.6, 115.6 (two peaks), 112.4 (two peaks), 77.5 (two peaks), 76.2, 75.8, 34.2, 34.0, 19.4 (two peaks), 18.9 (two peaks). Anal. Calcd for $C_{16}H_{15}FO_3$: C, 70.06; H, 5.51%. Found: C, 69.98; H, 5.43%.

7-(3,4-Dimethoxyphenyl)-2,3-dimethyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3d): Yield 59%; white solids; mp 137–138 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3055$, 2974, 2918, 2839, 1674, 1627, 1516, 1422, 1261, 1159, 1026 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 6.97 (t, $J = 2.2$ Hz, 1H), 6.93–6.87 (m, 1H), 6.84 (dd, $J = 8.2$, 1.4 Hz, 1H), 6.12 (s) and 6.07 (s) (total 1H), 5.35 (ddd, $J = 12.2$, 6.0, 4.0 Hz, 1H), 4.92 (dd, $J = 12.6$, 6.3 Hz, 1H), 3.93–3.82 (d, $J = 5.6$ Hz, 6H), 2.84 (ddd, $J = 25.2$, 17.6, 12.3 Hz, 1H), 2.54 (td, $J = 17.3$, 3.9 Hz, 1H), 1.75 (s, 3H), 1.44 (d, $J = 6.5$ Hz) and 1.37 (d, $J = 6.5$ Hz) (total 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 165.5, 165.1, 162.9, 162.6, 149.1 (two peaks), 130.8 (two peaks), 127.9, 127.5, 118.4 (two peaks), 112.5 (two peaks), 110.8 (two peaks), 109.2, 101.4, 101.0, 77.7 (two peaks), 76.4, 55.9 (two peaks), 34.2, 34.0, 19.3 (two peaks), 18.8 (two peaks). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37%. Found: C, 68.45; H, 6.27%.

2,3-Dimethyl-7-[4-(trifluoromethyl)phenyl]-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3e): Yield 60%; white solids; mp 135–136 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3047$, 2982, 2922, 2872, 1701, 1658, 1626, 1406, 1329, 1229, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, $J =$

8.3 Hz, 2H), 7.55 (d, $J = 8.1$ Hz, 2H), 6.10 (d, $J = 19.4$ Hz, 1H), 5.47 (dt, $J = 11.8$, 4.1 Hz, 1H), 4.94 (p, $J = 5.1$ Hz, 1H), 2.86–2.70 (m, 1H), 2.62 (ddd, $J = 17.4$, 8.5, 4.2 Hz, 1H), 1.75 (s, 2H), 1.62 (s, 1H), 1.46 (d, $J = 6.5$ Hz) and 1.37 (d, $J = 6.5$ Hz) (total 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.8, 164.5, 162.4, 162.0, 142.3 (two peaks), 130.8, 130.6, 128.2, 127.8, 126.1, 125.98–125.38 (multiple peaks), 112.33 (two peaks), 101.5, 77.9 (two peaks), 75.9, 75.5, 34.1, 33.9, 19.4 (two peaks), 18.9 (two peaks). Anal. Calcd for $C_{17}H_{15}F_3O_3$: C, 62.96; H, 4.66%. Found: C, 62.87; H, 4.71%.

3-[4-(Trifluoromethyl)phenyl]-3,4,6,7,8,9-hexahydropyrano[4,3-*b*]chromen-1(5a*H*)-one (3f): Yield 73%; white solids; mp 201–202 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3056$, 2951, 2939, 2864, 1699, 1622, 1413, 1337, 1163, 1064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, $J = 8.3$ Hz, 2H), 7.53 (d, $J = 8.5$ Hz, 2H), 6.01–5.94 (m, 1H), 5.45 (dd, $J = 12.0$, 4.1 Hz, 1H), 5.05 (ddd, $J = 16.8$, 11.4, 5.2 Hz, 1H), 2.81–2.68 (m, 1H), 2.63–2.49 (m, 1H), 2.40 (dd, $J = 14.1$, 1.9 Hz, 1H), 2.20–2.03 (m, 1H), 2.03–1.86 (m, 2H), 1.85–1.61 (m, 2H), 1.54–1.23 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.8 (two peaks), 163.4 (two peaks), 142.3, 131.5 (two peaks), 126.1 (two peaks), 125.6 (four peaks), 125.2, 122.5, 109.2, 108.9, 99.6, 99.3, 80.5, 80.3, 75.6 (two peaks), 35.0 (two peaks), 34.0, 33.0, 32.8, 26.8 (two peaks), 24.5 (two peaks). Anal. Calcd for $C_{19}H_{17}F_3O_3$: C, 65.14; H, 4.89%. Found: C, 65.11; H, 4.67%.

7-(4-Chlorophenyl)-2-(4-methoxyphenyl)-3-methyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3g): Yield 72%; white solids; mp 122–123 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3003$, 2941, 2908, 2839, 1703, 1629, 1512, 1400, 1253, 1159, 1064 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.24 (m, 6H), 6.94 (d, $J = 8.7$ Hz, 1H), 6.88 (d, $J = 8.7$ Hz, 1H), 6.41 (s) and 6.34 (s) (total 1H), 5.70 (d, $J = 16.5$ Hz, 1H), 5.40 (dd, $J = 10.6$, 5.0 Hz) and 5.30 (dd, $J = 12.0$, 4.0 Hz) (total 1H), 3.83 (d, $J = 11.7$ Hz, 3H), 2.78 (dd, $J = 17.5$, 12.0 Hz), 2.66–2.54 (m), and 2.44 (dd, $J = 17.5$, 4.0 Hz) (total 2H), 1.63 (d, $J = 3.9$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 165.0, 162.3, 161.9, 160.4 (two peaks), 136.8, 136.7, 134.3 (two peaks), 129.7 (two peaks), 129.5, 129.3, 128.8 (two peaks), 127.3 (two peaks), 125.9, 125.5, 114.2 (two peaks), 113.5 (two peaks), 101.2, 100.6, 82.9, 82.8, 75.9, 75.6, 55.3 (two peaks), 33.8 (two peaks), 19.3. Anal. Calcd for $C_{22}H_{19}ClO_4$: C, 69.02; H, 5.00%. Found: C, 69.12; H, 5.08%.

2-(4-Methoxyphenyl)-3-methyl-7-[4-(trifluoromethyl)-phenyl]-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3h): Yield 75%; yellowish solids; mp 63–64 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3059$, 2937, 2841, 1708, 1622, 1512, 1402, 1327, 1251, 1170, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, $J = 11.7$, 8.5 Hz, 2H), 7.49 (dd, $J = 12.0$, 8.2 Hz, 2H), 7.40–7.32 (m, 1H), 7.32–7.21 (m, 1H), 7.00–6.91 (m, 1H), 6.91–6.84 (m, 1H), 6.41 (s) and 6.35 (s) (total 1H), 5.71 (d, $J = 10.9$ Hz, 1H), 5.53–5.44 (m) and 5.39 (dd, $J = 11.9$, 4.0 Hz) (total 1H), 3.80 (d, $J = 12.8$ Hz, 3H), 2.78 (dd, $J = 17.4$, 11.9 Hz), 2.64 (d, $J = 7.2$ Hz), and 2.50 (dd, $J = 17.4$, 4.1 Hz) (total 2H), 1.64 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.7, 162.1, 161.8, 160.4, 142.2, 129.5 (three peaks), 126.19, 126.2, 125.8 (two peaks), 114.30 (two peaks), 113.44 (two peaks), 101.33, 82.9 (two peaks), 75.8, 75.4, 55.3 (two peaks), 33.8 (two peaks), 19.39. Anal. Calcd for $C_{23}H_{19}F_3O_4$: C, 66.34; H, 4.60%. Found: C, 63.15; H, 4.37%.

7-(3,4-Dimethoxyphenyl)-3-methyl-2-phenyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3i): Yield 80%; white solids; mp 90–91 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3068$, 2984, 2937, 2837, 1705, 1624, 1516, 1400, 1263, 1159, 1026 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53–7.30 (m, 5H), 7.05–6.75 (m, 3H), 6.38 (d, $J = 37.3$ Hz, 1H), 5.74 (d, $J = 10.9$ Hz, 1H), 5.37 (dd, $J = 11.9$, 4.0 Hz) and 5.28 (dd, $J = 12.2$, 3.9 Hz) (total 1H), 3.87 (dd, $J = 13.8$, 8.0 Hz, 6H), 2.86 (dd, $J = 17.4$, 12.2 Hz), 2.72 (dd, $J = 17.8$, 11.9 Hz), 2.55 (dd, $J = 17.9$, 4.1 Hz), and 2.44 (dd, $J = 17.5$, 3.9 Hz) (total 2H), 1.63 (d, $J = 4.4$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 165.5, 165.5, 162.4, 149.1 (two peaks), 137.8, 133.5, 130.5, 130.1, 129.42 (two peaks), 128.9 (two peaks), 128.4, 128.0, 127.8, 125.6, 125.2, 118.5, 118.3, 113.6, 110.8 (two peaks), 109.2 (two peaks), 101.1, 83.3, 83.2, 76.3, 55.9–55.7 (multiple peaks), 33.9 (two peaks), 31.5, 22.6, 19.37 (two peaks), 14.1. Anal. Calcd for $C_{23}H_{22}O_5$: C, 73.00; H, 5.86%. Found: C, 72.86; H, 5.85%.

3-Methyl-2-phenyl-7-[4-(trifluoromethyl)phenyl]-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3j): Yield 80%; white solids; mp 137–138 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3064$, 3028, 2914, 1707, 1665, 1626, 1402, 1337, 1159, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.55 (m, 2H), 7.55–7.40 (m, 5H), 7.40–7.29 (m, 2H), 6.41 (s) and 6.35 (s) (total 1H), 5.75 (d, $J = 8.3$ Hz, 1H), 5.50 (t, $J = 7.8$ Hz) and 5.41 (dd, $J = 12.0$, 4.1 Hz) (total 1H), 2.80 (dd, $J = 17.5$, 11.9 Hz), 2.66 (d, $J = 7.7$ Hz), and 2.52 (dd, $J = 17.5$, 4.2 Hz) (total 2H), 1.64 (d, $J = 15.9$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.7, 162.1, 161.8, 142.0, 137.6 (two peaks), 129.5 (two peaks), 129.0 (two peaks), 128.0, 127.8, 126.3–125.6 (multiple peaks), 125.6 (two peaks), 113.4 (two peaks), 101.3, 83.4, 83.2, 75.4, 33.8 (two peaks), 19.3. Anal. Calcd for $C_{22}H_{17}F_3O_3$: C, 68.39; H, 4.43%. Found: C, 68.44; H, 4.50%.

2-(4-Bromophenyl)-7-(4-chlorophenyl)-3-methyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3k): Yield 71%; white solids; mp 80–81 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3065$, 2972, 2912, 2853, 1699, 1624, 1491, 1398, 1294, 1155, 1070 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, $J = 8.4$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 1H), 7.43–7.19 (m, 6H), 6.39 (d, $J = 37.8$ Hz, 1H), 5.70 (d, $J = 16.0$ Hz, 1H), 5.40 (dd, $J = 10.9$, 4.8 Hz) and 5.31 (dd, $J = 12.0$, 4.0 Hz) (total 1H), 2.79 (dd, $J = 17.4$, 11.9 Hz), 2.61 (dd, $J = 13.2$, 7.9 Hz), and 2.45 (dd, $J = 17.5$, 4.0 Hz) (total 2H), 1.63 (d, $J = 4.1$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 161.8, 136.6, 136.5, 134.4, 132.2 (two peaks), 131.8, 131.6, 129.7, 129.6, 128.8 (two peaks), 127.3 (two peaks), 124.9, 123.7, 113.9 (two peaks), 100.9, 82.4, 82.2, 76.0, 75.6, 33.7, 19.3. Anal. Calcd for $C_{21}H_{16}BrClO_3$: C, 58.42; H, 3.74%. Found: C, 58.98; H, 3.48%.

7-(3-Chlorophenyl)-3-methyl-2-(4-nitrophenyl)-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3l): Yield 76%; white solids; mp 150–151 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3066$, 2941, 2918, 2850, 1712, 1631, 1518, 1337, 1398, 1350, 1155, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34–8.26 (m, 1H), 8.26–8.18 (m, 1H), 7.67–7.59 (m, 1H), 7.56–7.48 (m, 1H), 7.44–7.17 (m, 4H), 6.47 (s) and 6.41 (d, $J = 0.6$ Hz)

(total 1H), 5.83 (d, $J = 15.2$ Hz, 1H), 5.42 (t, $J = 7.7$ Hz), and 5.32 (dd, $J = 12.0$, 4.0 Hz) (total 1H), 2.83 (dd, $J = 17.6$, 12.0 Hz), 2.66 (d, $J = 7.6$ Hz), and 2.50 (dd, $J = 17.6$, 4.1 Hz) (total 2H), 1.65 (dd, $J = 14.3$, 8.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.3, 164.1, 161.9, 161.5, 148.4, 144.1 (two peaks), 139.9 (two peaks), 134.6 (two peaks), 129.9 (two peaks), 128.82 (two peaks), 126.8 (two peaks), 124.7, 124.4–123.9 (multiple peaks), 123.9 (two peaks), 114.5 (two peaks), 101.7, 101.1, 81.7, 81.4, 75.6 (two peaks), 75.5, 33.6 (two peaks), 19.3. Anal. Calcd for $C_{21}H_{16}ClNO_5$: C, 63.40; H, 4.05; N, 3.52%. Found: C, 63.41; H, 4.09; N, 3.47%.

Crystallographic data have been deposited with The Cambridge Crystallographic Data Centre: Deposition number CCDC-931766 for compound **3l**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif (or from The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; e-mail: data_request@ccdc.cam.ac.uk).

7-(4-Chlorophenyl)-3-methyl-2-(4-nitrophenyl)-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3m): Yield 80%; white solids; mp 163–164 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3072$, 2970, 2924, 2853, 1714, 1622, 1519, 1392, 1364, 1286, 1151, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33–8.18 (m, 2H), 7.63 (d, $J = 8.7$ Hz, 1H), 7.58–7.50 (m, 1H), 7.41–7.21 (m, 4H), 6.46 (s) and 6.40 (s) (total 1H), 5.83 (d, $J = 12.3$ Hz, 1H), 5.42 (dd, $J = 10.3$, 5.4 Hz) and 5.33 (dd, $J = 11.9$, 4.0 Hz) (total 1H), 2.83 (dd, $J = 17.6$, 11.9 Hz), 2.64 (t, $J = 7.0$ Hz), and 2.48 (dd, $J = 17.6$, 4.0 Hz) (total 2H), 1.64 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.5, 164.2, 161.9, 161.6, 148.4, 144.2 (two peaks), 136.4 (two peaks), 134.5, 128.8 (two peaks), 127.27, 124.74, 124.4–124.0 (multiple peaks), 114.5 (two peaks), 101.6, 101.1, 81.7, 81.5, 76.0, 75.6, 33.7 (two peaks), 19.3. Anal. Calcd for $C_{21}H_{16}ClNO_5$: C, 63.40; H, 4.05; N, 3.52%. Found: C, 63.41; H, 3.90; N, 3.46%.

7-(4-Methoxyphenyl)-3-methyl-2-(4-nitrophenyl)-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3n): Yield 73%; white solids; mp 150–151 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3055$, 2933, 2908, 2839, 1708, 1628, 1523, 1394, 1350, 1244, 1153, 1057 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33–8.26 (m, 1H), 8.26–8.19 (m, 1H), 7.66–7.59 (m, 1H), 7.57–7.50 (m, 1H), 7.32–7.21 (m, 2H), 6.92–6.81 (m, 2H), 6.47 (s) and 6.41 (s) (total 1H), 5.82 (d, $J = 14.1$ Hz, 1H), 5.40 (dd, $J = 11.1$, 4.4 Hz) and 5.29 (dd, $J = 12.0$, 4.0 Hz) (total 1H), 3.79 (d, $J = 0.5$ Hz, 3H), 2.88 (dd, $J = 17.6$, 12.0 Hz), 2.76–2.55 (m), and 2.44 (dd, $J = 17.6$, 4.0 Hz) (total 2H), 1.65 (d, $J = 3.9$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9, 164.6, 162.3, 161.9, 159.8, 148.4, 144.3 (two peaks), 129.9 (two peaks), 128.8 (two peaks), 127.4 (two peaks), 124.5, 124.1 (three peaks), 114.6 (two peaks), 113.9 (two peaks), 101.6, 101.1, 81.6, 81.4, 76.2, 55.2, 33.6, 19.2. Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56%. Found: C, 67.30; H, 4.71; N, 3.50%.

7-(3,4-Dimethoxyphenyl)-3-methyl-2-(4-nitrophenyl)-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3o): Yield 74%; white solids; mp 152–153 °C (from ethyl acetate–hexane); IR (KBr): $\nu_{max} = 3072$, 2937, 2914, 2839, 1701, 1633, 1521, 1398, 1341, 1259, 1157, 1058 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32–8.26 (m, 1H), 8.26–8.19 (m, 1H), 7.67–7.60 (m, 1H), 7.58–7.51 (m, 1H), 6.92 (dd, $J = 3.6$, 1.9 Hz, 1H), 6.90–6.75 (m, 2H), 6.47 (s) and 6.41 (s) (total 1H), 5.83 (d, $J = 11.2$ Hz, 1H), 5.39 (dd, $J = 11.4$, 4.2 Hz) and 5.29 (dd, $J = 12.1$, 3.9 Hz) (total 1H), 3.86 (t, $J = 2.8$ Hz, 6H), 2.89 (dd, $J = 17.6$, 12.1 Hz), 2.72 (dd, $J = 17.9$, 11.4 Hz), 2.59 (dd, $J = 17.9$, 4.3 Hz), and 2.45 (dd, $J = 17.6$, 4.0 Hz) (total 2H), 1.65 (d, $J = 3.7$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9, 164.6, 162.3, 161.9, 149.1 (two peaks), 148.4, 144.3 (two peaks), 130.3 (two peaks), 128.8 (two peaks), 124.5, 124.2 (two peaks), 118.3, 114.6, 110.7 (two peaks), 109.1 (two peaks), 101.59, 101.1, 81.5 (two peaks), 76.3, 55.8 (two peaks), 33.7 (two peaks), 19.2. Anal. Calcd for $C_{23}H_{21}NO_7$: C, 65.24; H, 5.00; N, 3.31%. Found: C, 65.23; H, 4.83; N, 3.22%.

7-(3-Bromophenyl)-3-methyl-2-(4-nitrophenyl)-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3p): Yield 71%; white solid; mp 160–161 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3082$, 2956, 2916, 2844, 1707, 1629, 1521, 1396, 1384, 1286, 1155, 1058 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33–8.26 (m, 1H), 8.26–8.19 (m, 1H), 7.66–7.59 (m, 1H), 7.56–7.49 (m, 2H), 7.49–7.42 (m, 1H), 7.33–7.17 (m, 2H), 6.47 (s) and 6.41 (d, $J = 0.6$ Hz) (total 1H), 5.83 (d, $J = 15.2$ Hz, 1H), 5.46–5.37 (m) and 5.32 (dd, $J = 12.0$, 4.0 Hz) (total 1H), 2.83 (dd, $J = 17.6$, 12.0 Hz), 2.65 (d, $J = 7.6$ Hz), and 2.49 (dd, $J = 17.6$, 4.1 Hz) (total 2H), 1.65 (dd, $J = 13.4$, 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.3, 164.1, 161.9, 161.5, 148.4, 144.1 (two peaks), 140.1 (two peaks), 131.7 (two peaks), 130.2 (two peaks), 128.96 (two peaks), 128.7, 124.7, 124.3 (two peaks), 122.7, 114.5 (two peaks), 101.7, 101.1, 81.7, 81.4, 75.7, 75.4, 33.6 (two peaks), 19.3. Anal. Calcd for $C_{21}H_{16}BrNO_5$: C, 57.03; H, 3.65; N, 3.17%. Found: C, 57.05; H, 3.43; N, 3.51%.

Methyl 4-{3-Methyl-5-oxo-7-[4-(trifluoromethyl)phenyl]-2,5,7,8-tetrahydropyrano[4,3-*b*]pyran-2-yl}benzoate (3q): Yield 76%; white solids; mp 158–159 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3061$, 2955, 2914, 1708, 1633, 1398, 1284, 1166 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13–8.08 (m, 1H), 8.06–8.01 (m, 1H), 7.62 (dd, $J = 19.1$, 8.2 Hz, 2H), 7.55–7.45 (m, 3H), 7.44–7.39 (m, 1H), 6.44 (s) and 6.38 (s) (total 1H), 5.79 (d, $J = 17.1$ Hz, 1H), 5.51 (dd, $J = 9.1$, 6.4 Hz) and 5.41 (dd, $J = 11.9$, 4.1 Hz) (total 1H), 3.94 (d, $J = 11.1$ Hz, 3H), 2.86–2.77 (m), 2.69–2.63 (m), and 2.52 (dd, $J = 17.5$, 4.1 Hz) (total 2H), 1.64 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.4 (two peaks), 164.5, 164.2, 161.9, 161.6, 142.1 (two peaks), 131.2 (two peaks), 130.3 (two peaks), 127.9, 127.7, 126.1 (two peaks), 126.0–125.3 (multiple peaks), 125.0, 113.9 (two peaks), 101.5, 82.6, 82.4, 75.8, 75.4, 52.3 (two peaks), 33.7 (two peaks), 19.3 (two peaks). Anal. Calcd for $C_{24}H_{19}F_3O_5$: C, 64.86; H, 4.31%. Found: C, 64.68; H, 4.27%.

2-(4-Chlorophenyl)-3-methyl-7-[4-(trifluoromethyl)phenyl]-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (3r): Yield 75%; white solids; mp 75–76 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3057$, 2926, 2874, 1699, 1627, 1508, 1400, 1329, 1292, 1166 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (dd, $J = 15.2$, 8.3 Hz, 2H), 7.53–7.45 (m, 2H), 7.41 (s, 1H), 7.39 (s, 1H), 7.35 (d, $J = 8.5$ Hz, 1H), 7.29 (d, $J = 8.5$ Hz, 1H), 6.43 (s) and 6.37 (s) (total 1H), 5.72 (d, $J = 16.2$ Hz, 1H), 5.49 (t, $J = 7.8$ Hz) and 5.40 (dd, $J = 11.9$, 4.0 Hz) (total 1H), 2.80 (dd, $J = 17.5$, 11.9 Hz), 2.64 (d, $J = 7.7$ Hz), and 2.50 (dd, $J =$

17.5, 4.1 Hz) (total 2H), 1.64 (d, $J = 5.2$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.6, 164.1, 161.6, 142.1, 141.9, 135.9 (two peaks), 135.5 (two peaks), 129.3 (two peaks), 126.1 (two peaks), 125.9–125.4 (multiple peaks), 125.1, 113.9 (two peaks), 101.5, 100.9, 82.4, 82.2, 75.8, 75.4, 33.8 (two peaks), 31.5, 22.6, 19.3, 14.2. Anal. Calcd for $C_{22}H_{16}ClF_3O_3$: C, 62.79; H, 3.83%. Found: C, 62.62; H, 3.58%.

3,6-Bis(4-chlorophenyl)-7-methyl-3,4,5,6-tetrahydro-1*H*-isochromen-1-one (3s): Yield 68%; white solids; mp 131–132 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3068$, 2931, 2910, 1608, 1489, 1398, 1296, 1157 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44–7.23 (m, 8H), 6.42 (s) and 6.36 (s) (total 1H), 5.71 (d, $J = 16.2$ Hz, 1H), 5.40 (dd, $J = 10.8$, 4.8 Hz) and 5.31 (dd, $J = 11.9$, 4.0 Hz) (total 1H), 2.79 (dd, $J = 17.5$, 12.0 Hz), 2.68–2.53 (m), 2.45 (dd, $J = 17.5$, 4.0 Hz) (total 2H), 1.63 (d, $J = 4.5$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.8, 164.5, 162.1, 161.7, 136.6, 136.5, 136.0 (two peaks), 135.4 (two peaks), 134.4, 129.4, 129.3–129.1 (multiple peaks), 128.8 (two peaks), 127.3 (two peaks), 125.4, 125.0, 113.9 (two peaks), 101.4, 100.9, 82.3, 82.2, 76.0, 75.6, 33.8, 19.3. Anal. Calcd for $C_{21}H_{16}Cl_2O_3$: C, 65.13; H, 4.16%. Found: C, 65.46; H, 4.92%.

The compounds **7a**–**7d**, **11a**–**11d**, **13a**, and **13b** were prepared in the same manner as described for **3a**.

3-Methyl-2-(4-nitrophenyl)-7,7-diphenyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (7a): Yield 73%; yellowish solids; mp 104–105 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3059$, 2912, 2856, 1708, 1633, 1523, 1398, 1346, 1228, 1166 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17–8.10 (m, 2H), 7.43–7.13 (m, 12H), 6.32 (d, $J = 0.6$ Hz, 1H), 5.74 (s, 1H), 3.31 (d, $J = 17.4$ Hz, 1H), 3.16 (d, $J = 17.4$ Hz, 1H), 1.58 (d, $J = 0.6$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.1, 161.6, 148.3, 144.3, 142.8, 142.2, 128.8–128.3 (multiple peaks), 127.9 (two peaks), 125.4 (two peaks), 124.0 (two peaks), 114.1, 102.4, 84.1, 81.6, 37.1, 19.0. Anal. Calcd for $C_{27}H_{21}NO_5$: C, 73.79; H, 4.82; N, 3.19%. Found: C, 73.71; H, 4.87; N, 3.14%.

2-(4-Methoxyphenyl)-3-methyl-7,7-diphenyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (7b): Yield 68%; greenish solids; mp 128–129 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3059$, 2931, 2835, 1693, 1631, 1512, 1302, 1255, 1170 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (dd, $J = 8.3$, 1.0 Hz, 2H), 7.34–7.13 (m, 10H), 6.85–6.81 (m, 2H), 6.23 (s, 1H), 5.64 (s, 1H), 3.84 (s, 3H), 3.23 (d, $J = 17.6$ Hz, 1H), 3.12 (d, $J = 17.6$ Hz, 1H), 1.56 (d, $J = 7.8$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.5, 161.9, 160.2, 143.4, 142.5, 130.1, 129.3, 128.4 (two peaks), 127.6 (two peaks), 125.8, 125.4, 125.1, 114.1, 113.2, 102.0, 83.9, 82.9, 55.3, 37.3, 19.2. Anal. Calcd for $C_{28}H_{24}O_4$: C, 79.22; H, 5.70%. Found: C, 79.23; H, 5.73%.

2-(4-Chlorophenyl)-3-methyl-7,7-diphenyl-7,8-dihydropyrano[4,3-*b*]pyran-5(2*H*)-one (7c): Yield 75%; white solids; mp 70–71 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3061$, 2924, 2854, 1708, 1633, 1448, 1398, 1230, 1166 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (dd, $J = 5.6$, 3.7 Hz, 3H), 7.33–7.23 (m, 5H), 7.23–7.16 (m, 4H), 7.13 (d, $J = 8.4$ Hz, 2H), 6.27 (s, 1H), 5.64 (s, 1H), 3.25 (d, $J = 17.5$ Hz, 1H), 3.13 (d, $J = 17.5$ Hz, 1H), 1.57 (d, $J = 9.8$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.3, 161.7, 143.2, 142.3, 136.2, 135.2, 129.2, 128.4 (two peaks), 128.3, 127.7 (two peaks), 125.7, 125.4 (two peaks), 124.5, 113.7, 82.2, 37.2, 19.1. Anal. Calcd for $C_{27}H_{21}ClO_3$: C, 75.61; H, 4.94%. Found: C, 75.43; H, 5.19%.

Methyl 4-(3-Methyl-5-oxo-7,7-diphenyl-2,5,7,8-tetrahydropyrano[4,3-*b*]pyran-2-yl)benzoate (7d): Yield 72%; white solids; mp 174–175 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3061$, 2999, 2910, 1705, 1633, 1400, 1286, 1197 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00–7.95 (m, 2H), 7.36 (dd, $J = 8.3$, 1.1 Hz, 2H), 7.34–7.16 (m, 10H), 6.26 (s, 1H), 5.71 (s, 1H), 3.95 (s, 3H), 3.27 (d, $J = 17.5$ Hz, 1H), 3.15 (d, $J = 17.5$ Hz, 1H), 1.55 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 166.5, 164.3, 161.8, 143.1, 142.5, 142.3, 130.9, 130.1, 128.4 (two peaks), 127.9–127.7 (multiple peaks), 125.7, 125.43, 124.4, 113.6, 102.1, 84.0, 82.5, 52.3, 37.2, 19.1. Anal. Calcd for $C_{29}H_{24}O_5$: C, 76.98; H, 5.35%. Found: C, 76.92; H, 5.29%.

***tert*-Butyl 7-(4-Chlorophenyl)-3-methyl-2-(4-nitrophenyl)-5-oxo-7,8-dihydro-2*H*-pyrano[3,2-*c*]pyridine-6(5*H*)-carboxylate (11a):** Yield 71%; white solids; mp 87–88 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3072$, 2982, 2935, 1708, 1606, 1525, 1492, 1348, 1286, 1151, 1012 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.30–8.17 (m, 1H), 8.06–7.96 (m, 1H), 7.58–7.48 (m, 1H), 7.33–7.27 (m, 1H), 7.22–7.17 (m, 1H), 7.17–7.11 (m, 2H), 7.02 (d, $J = 8.3$ Hz, 1H), 6.46 (d, $J = 1.7$ Hz, 1H), 5.63 (d, $J = 20.0$ Hz, 1H), 5.55 (dd, $J = 24.5$, 5.1 Hz, 1H), 3.25 (dd, $J = 17.1$, 6.2 Hz) and 3.05 (dd, $J = 18.0$, 6.7 Hz) (total 1H), 2.56 (d, $J = 17.0$ Hz) and 2.48 (dd, $J = 17.1$, 2.1 Hz) (total 1H), 1.61 (d, $J = 12.6$ Hz, 3H), 1.50 (d, $J = 1.3$ Hz, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 163.1, 162.6, 159.5, 144.4, 138.8, 133.5, 128.8 (two peaks), 128.5, 128.0, 126.9 (two peaks), 124.1 (three peaks), 123.8, 114.6, 114.0, 83.4 (two peaks), 81.3, 81.0, 54.5, 54.3, 33.5, 33.3, 28.2, 28.0 (two peaks), 19.2 (two peaks). Anal. Calcd for $C_{26}H_{25}ClN_2O_6$: C, 62.84; H, 5.07; N, 5.64%. Found: C, 62.60; H, 4.92; N, 5.59%.

***tert*-Butyl 7-(4-Chlorophenyl)-2-(4-methoxyphenyl)-3-methyl-5-oxo-7,8-dihydro-2*H*-pyrano[3,2-*c*]pyridine-6(5*H*)-carboxylate (11b):** Yield 69%; white solids; mp 83–84 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3072$, 2978, 2839, 1712, 1681, 1512, 1398, 1298, 1138 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32–7.24 (m, 2H), 7.21–7.13 (m, 2H), 7.04 (d, $J = 8.2$ Hz, 1H), 6.95–6.86 (m, 2H), 6.72–6.67 (m, 1H), 6.39 (s, 1H), 5.58–5.47 (m, 2H), 3.81 (d, $J = 6.6$ Hz, 3H), 3.20 (dd, $J = 17.1$, 6.2 Hz) and 3.03 (dd, $J = 18.0$, 6.7 Hz) (total 1H), 2.56–2.49 (m) and 2.46 (dd, $J = 17.1$, 2.1 Hz) (total 1H), 1.57 (d, $J = 10.3$ Hz, 3H), 1.51 (d, $J = 3.1$ Hz, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 159.3, 153.0 (two peaks), 130.4, 130.0, 129.4, 128.7 (two peaks), 128.5, 127.1 (two peaks), 125.5, 114.1, 113.9, 113.5, 112.8, 83.1 (two peaks), 82.6, 82.3, 55.3 (two peaks), 54.4 (two peaks), 33.5, 33.2, 28.0, 19.3 (two peaks). Anal. Calcd for $C_{27}H_{28}ClNO_5$: C, 67.28; H, 5.86; N, 2.91%. Found: C, 67.20; H, 5.53; N, 2.84%.

***tert*-Butyl 7-(4-Chlorophenyl)-3-methyl-5-oxo-2-phenyl-7,8-dihydro-2*H*-pyrano[3,2-*c*]pyridine-6(5*H*)-carboxylate (11c):** Yield 62%; white solids; mp 80–81 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3063$, 2980, 2931, 1712, 1629, 1492, 1396, 1296, 1138, 1089 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42–7.34 (m, 3H), 7.32–7.24 (m, 2H), 7.22–7.12 (m, 2H), 7.06–6.97 (m, 2H), 6.40 (s) and 6.26 (d, $J = 15.9$ Hz) (total 1H), 5.59–5.53 (m) and 5.51 (d, $J = 5.8$ Hz) (total 2H), 3.21 (dd, $J = 17.2$, 6.3 Hz) and 3.05 (dd, $J = 17.9$, 6.7 Hz)

(total 1H), 2.50 (ddd, $J = 36.8$, 17.6, 1.7 Hz, 1H), 1.57 (d, $J = 8.4$ Hz, 3H), 1.51 (d, $J = 4.0$ Hz, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 163.4, 162.8, 159.9, 159.4, 128.3, 127.8 (two peaks), 127.25–127.01 (multiple peaks), 126.7, 125.3, 125.1, 113.5, 112.9, 105.6, 105.3, 83.1 (two peaks), 82.9, 82.6, 60.3, 54.4 (two peaks). Anal. Calcd for $C_{26}H_{26}ClNO_4$: C, 69.10; H, 5.80; N, 3.10%. Found: C, 68.90; H, 5.71; N, 2.98%.

***tert*-Butyl 7-(4-Chlorophenyl)-2,3-dimethyl-5-oxo-7,8-dihydro-2*H*-pyrano[3,2-*c*]pyridine-6(5*H*)-carboxylate (11d):** Yield 72%; white solids; mp 140–141 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3028$, 2980, 2929, 1712, 1674, 1494, 1413, 1300, 1139 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 7.15 (t, $J = 9.1$ Hz, 2H), 6.17 (s) and 6.10 (s) (total 1H), 5.55 (d, $J = 6.4$ Hz, 1H), 4.80–4.71 (m, 1H), 3.25–3.14 (m, 1H), 2.60–2.49 (m, 1H), 1.69 (s, 3H), 1.49 (d, $J = 11.5$ Hz, 9H), 1.30 (d, $J = 6.5$ Hz) and 1.14 (d, $J = 6.5$ Hz) (total 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 163.4, 163.0, 160.0, 159.5, 153.1, 139.0 (two peaks), 133.2, 128.6 (two peaks), 127.6, 127.1 (two peaks), 112.6, 112.2, 106.0, 83.0 (two peaks), 54.5, 54.3, 33.4, 33.2, 28.0 (two peaks), 19.1 (two peaks), 18.9, 18.7. Anal. Calcd for $C_{21}H_{24}ClNO_4$: C, 64.69; H, 6.20; N, 3.59%. Found: C, 64.70; H, 6.20; N, 3.55%.

3,6-Dimethyl-2-(4-nitrophenyl)-2*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-one (13a): Yield 95%; greenish solids; mp 170–171 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3080$, 2910, 2856, 1666, 1633, 1521, 1396, 1346, 1182 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.23–8.15 (m, 2H), 7.80 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.67–7.58 (m, 2H), 7.51 (ddd, $J = 8.6$, 7.2, 1.5 Hz, 1H), 7.32–7.24 (m, 1H), 7.19–7.13 (m, 1H), 6.90–6.85 (m, 1H), 5.95 (s, 1H), 3.69 (s, 3H), 1.82 (d, $J = 0.5$ Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.5, 152.7, 148.2, 145.0, 139.0, 130.9, 128.5, 127.3, 124.0, 122.6, 121.9, 116.2, 115.2, 114.1, 106.5, 80.2, 29.4, 19.7. Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04%. Found: C, 69.05; H, 4.63; N, 8.04%.

3,6-Dimethyl-2-phenyl-2*H*-pyrano[3,2-*c*]quinolin-5(6*H*)-one (13b): Yield 92%; white solids; mp 162–163 °C (from ethyl acetate–hexane); IR (KBr): $\nu = 3074$, 2972, 2928, 1654, 1633, 1587, 1452, 1398, 1111 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83 (dd, $J = 8.0$, 1.4 Hz, 1H), 7.51–7.42 (m, 3H), 7.36–7.31 (m, 3H), 7.29–7.25 (m, 1H), 7.17–7.11 (m, 1H), 6.85–6.79 (m, 1H), 5.88 (s, 1H), 3.69 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.8, 153.0, 138.9, 138.3, 130.4, 128.9, 128.7 (two peaks), 127.7, 122.8, 121.6, 115.6, 115.2, 113.9, 106.5, 81.7, 29.3, 19.8. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62%. Found: C, 79.13; H, 4.48; N, 4.57%.

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Supporting Information

Spectral data including ^{1}H NMR and ^{13}C NMR spectra of **3a**–**3s**, **7a**–**7d**, **11a**–**11d**, **13a**, and **13b** are provided. This material is available free of charge on the Web at: http://www.csj.jp/journals/bcsj/.

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