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# Stereoselective hetero-Diels–Alder reaction of 3-(polyfluoroacyl)chromones with enol ethers. Novel synthesis of 2-$R^F$-containing nicotinic acid derivatives

Vyacheslav Ya. Sosnovskikh [a,*], Igor A. Khalymbadzha [a], Roman A. Irgashev [a], Pavel A. Slepukhin [b]

[a] Department of Chemistry, Ural State University, 620083 Ekaterinburg, Russian Federation
[b] Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620041 Ekaterinburg, Russian Federation

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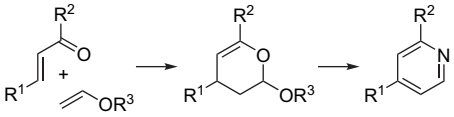
ABSTRACT

3-(Polyfluoroacyl)chromones undergo heterodiene cycloaddition to 3,4-dihydro-2*H*-pyran, 2,3-dihydrofuran and ethyl vinyl ether under mild conditions, producing novel fused pyrans with high stereoselectivity and in good yields. Some of these pyrans were transformed into 2-$R^F$-containing pyridines on treatment with ammonium acetate in ethanol.



## 1. Introduction

It is known that cycloaddition between α,β-unsaturated ketones and vinyl ethers affords the corresponding 2-alkoxydihydropyrans,[1] which can be considered as 1,5-dicarbonyl compounds in protected form and represent an important class of organic compounds. Employment of such protected substrates for the preparation of substituted pyridines[2] makes them useful synthetic intermediates (Scheme 1).



**Scheme 1.**

3-Acylchromones **1** and trifluoroacetylated ether **2** on reaction with alkyl vinyl ethers also can act as heterodienes in an inverse electron-demand Diels–Alder reaction.[3] However, cycloaddition involving these substrates often requires prolonged heating and occurs with low stereoselectivity affording mixtures of *endo*- and *exo*-adducts with the former predominating.[4,5] For example, the reaction of 3-formylchromone **1** (R=H) with 3,4-dihydro-2*H*-pyran was carried out in a sealed tube at 115 °C for 5 days to give tetracyclic system **3** (R=H) as a mixture of two stereoisomers in approximately equal amounts in 40% yield.[4] A similar reaction between 4-ethoxy-1,1,1-trifluorobut-3-en-2-one **2** and 2,3-dihydrofuran at 80 °C for 30 h afforded a diastereomeric mixture of tetrahydrofuropyran **4** in 68% yield.[5] Published data on the participation of 3-(polyfluoroacyl)chromones **1** (R=$R^F$), whose structure combines a heterocyclic moiety and $R^FCO$ substituent, in hetero-Diels–Alder reactions are lacking (Fig. 1). This polyfluoroacylated chromone system appeared to be a useful heterodiene for the simple and convenient synthesis of fused $R^F$-containing pyrans and pyridines, which could be used for the preparation of more complex molecules.

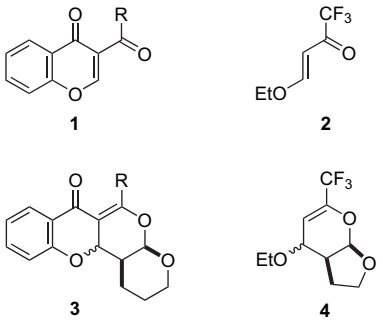


**Figure 1.**

* Corresponding author. Fax: +7 343 261 59 78.
*E-mail addresses:* vyacheslav.sosnovskikh@usu.ru, svy@etel.ru (V.Ya. Sosnovskikh).

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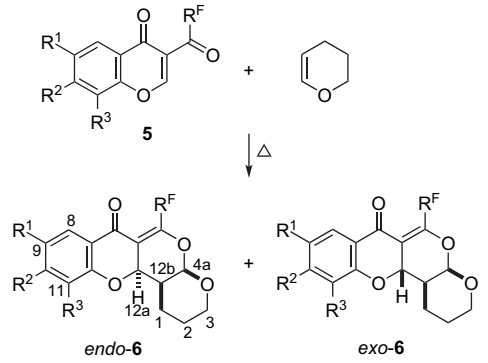
In continuation of our studies on the synthetic potential of 3-(polyfluoroacyl)chromones **5**, which turned out to be highly reactive $R^F$-containing substrates in reactions with mono- and dinucleophiles,[6] and owing to the increasing importance of fluorine-containing heterocycles in biology, pharmacology and industrial applications,[7] we decided to investigate their reaction with cyclic vinyl ethers, namely, 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran, as well as with ethyl vinyl ether. Bearing in mind the electron-withdrawing force of a polyfluoroalkyl group and the fact that hetero-Diels–Alder reactions are facilitated by the presence of electron-donating groups in the dienophile and of electron-withdrawing groups in the heterodiene, it was of interest to elucidate the effects of structural features of 3-$R^F$CO-chromones **5** on the occurrence and stereoselectivity of [4+2] cycloadditions compared to those of non-fluorinated chromones **1** and the linear analogue **2**. In addition to our preliminary communication,[8] some novel fused pyrans and pyridines bearing $R^F$ groups have been prepared.

## 2. Results and discussion

We found that 3-$R^F$CO-chromones **5** reacted with a 10-fold excess of 3,4-dihydro-2*H*-pyran without solvent at 85 °C for 4 h (with **5a**–**e**) or at ~20 °C for 2 days (with **5f**) and gave cycloadducts **6a**–**f** in 27–78% yields (Scheme 2). The results of a series of heterodiene cycloadditions of chromones **5** to 3,4-dihydro-2*H*-pyran are summarized in Table 1. The regio- and stereochemistry of these adducts can be explained by assuming that [4+2] inverse electron-demand cycloaddition of 3,4-dihydro-2*H*-pyran over the enone system of chromones **5** occurs regioselectively such that the oxygen atom of dienophile is located at the 4a-position and from an *endo* transition state, which would account for the *cis*/*cis* stereochemistry observed between the H-12a, H-12b, and H-4a atoms in the newly formed ring (for X-ray diffraction data, see below).




Scheme 2.

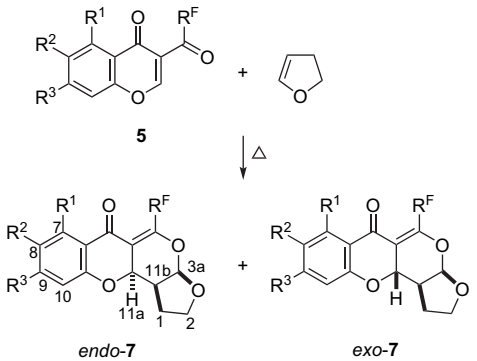
Unlike cycloaddition reactions involving 3-acylchromones **1** and trifluoromethyl ketone **2** that occur under more drastic conditions and with low stereoselectivity,[4,5] compounds **6a**–**f** were formed almost exclusively as the *endo*-isomers. The appearance of *exo*-adducts in 3–4% ($^1$H NMR spectral data) was observed only in the case of the more reactive chromones **5e**,**f** with electron-withdrawing substituents at C-6 of the aromatic ring. Interestingly, replacement of the trifluoromethyl group with difluoromethyl had no effect on the *endo*-selectivity (cf. **6a** and **6b**), however, the absence of the $R^F$ group decreases *endo*-selectivity considerably (cf. **6f** and **6h**, **6g** and **6i**). Note that the cycloaddition between **5d** and 3,4-dihydro-2*H*-pyran was disfavoured (yield 27%), presumably because of the greater electronic density present in the aryl ring of the electrophilic counterpart. The results obtained for 3,4-dihydro-2*H*-pyran show that the electron-withdrawing $CF_3$ and $CF_2H$ groups in chromones **5** favour both the rate and stereoselectivity of heterodiene cycloaddition. 3-(2,2,3,3-Tetrafluoropropanoyl)chromones **5j**,**k** also participated in the reaction with 3,4-dihydro-2*H*-pyran (2 equiv) at ~60 °C for 4 h, affording cycloadducts **6j**,**k**, however, no stereoselectivity was found in this case. The observed difference in reactivity between **5** and the above-mentioned non-fluorinated chromones **1** is undoubtedly due to the fact that the presence of the powerful electron-withdrawing $R^F$ group in place of H or Me on the 3-acyl moiety makes the chromone **5** more reactive mainly by lowering the energy level of the LUMO.

**Table 1**
Synthesis of fused pyrans **6a**–**k** by reaction of chromones **5a**–**k** with 3,4-dihydro-2*H*-pyran

| Chromone | $R^F$ | $R^1$ | $R^2$ | $R^3$ | Adduct | Ratio of *endo*/*exo* | Yield (%) |
|---|---|---|---|---|---|---|---|
| **5a** | $CF_2H$ | H | H | H | **6a** | 100:0 | 52 |
| **5b** | $CF_3$ | H | H | H | **6b** | 100:0 | 42 |
| **5c** | $CF_3$ | Me | H | H | **6c** | 100:0 | 51 |
| **5d** | $CF_3$ | H | MeO | H | **6d** | 100:0 | 27 |
| **5e** | $CF_3$ | Cl | H | H | **6e** | 97:3 | 73 |
| **5f** | $CF_3$ | $NO_2$ | H | H | **6f** | 96:4 | 78 |
| **5g** | $CF_3$ | Br | H | Br | **6g** | 60:40 | 63 |
| **5h** | H | $NO_2$ | H | H | **6h** | 55:45 | 62 |
| **5i** | H | Br | H | Br | **6i** | 10:90 | 35 |
| **5j** | $(CF_2)_2H$ | H | H | H | **6j** | 47:53 | 56 |
| **5k** | $(CF_2)_2H$ | Me | H | H | **6k** | 47:53 | 31 |

As pointed out by numerous authors, *endo* attack of the enol ether was favoured owing to LUMO–HOMO interactions between the carbonyl group and the vinyl ether.[3,4] At the same time, it is commonly known that *exo*-isomers are thermodynamically more stable due to the anomeric effect.[4,9,10] Our attempts to isomerize *endo*-**6c** to *exo*-**6c** by refluxing for 3–4 h in diethyl ether in the presence of $CF_3CO_2H$ or in ethanol with piperidine and acetic acid failed. In all cases, *endo*-**6c** was returned in a decreased amount due to partial retro-cycloaddition.[10] However, when ethanol was replaced by pinacoline, we obtained a mixture of composition *endo*-**6c**/*exo*-**6c**=66:34, which made it possible to obtain a qualitative $^1$H NMR spectrum of *exo*-**6c**. Epimerization at C-12a probably proceeds through the 1,4-addition of a piperidine molecule followed by pyrone ring opening to form an intermediate, which can recyclize to give either configuration at this atom.

In the same way, chromones **5a**–**d**,**j**–**l** reacted with 2,3-dihydrofuran (2 equiv) to produce the cycloaddition products **7a**–**d**,**j**–**l**. All of these reactions proceeded under milder conditions (60 °C, 4 h) but with lower *endo*-selectivity (69–97% for $R^F$=$CF_2H$, $CF_3$ and 54–60% for $R^F$=$(CF_2)_2H$) (Scheme 3, Table 2).




Scheme 3.

Structures of adducts **6** and **7** were determined on the basis of spectral data in the light of the literature data on related systems.[4] The most important features of the $^1$H NMR spectra of compounds **6** are the signals appearing in their aliphatic region due to the H-4a

**Table 2**
Synthesis of fused pyrans **7a–d,j–l** by reaction of chromones **5a–d,j–l** with 2,3-dihydrofuran

| Chromone | $R^F$ | $R^1$ | $R^2$ | $R^3$ | Adduct | Ratio of *endo*/*exo* | Yield (%) |
|---|---|---|---|---|---|---|---|
| **5a** | $CF_2H$ | H | H | H | **7a** | 97:3 | 51 |
| **5b** | $CF_3$ | H | H | H | **7b** | 70:30 | 69 |
| **5c** | $CF_3$ | H | Me | H | **7c** | 69:31 | 68 |
| **5d** | $CF_3$ | H | H | MeO | **7d** | 93:7 | 53 |
| **5j** | $(CF_2)_2H$ | H | H | H | **7j** | 60:40 | 36 |
| **5k** | $(CF_2)_2H$ | H | Me | H | **7k** | 54:46 | 63 |
| **5l** | $CF_3$ | Me | H | Me | **7l** | 93:7 | 26 |

and H-12a protons. The $^1$H NMR spectra of *endo*-cycloadducts **6a–f** in $CDCl_3$ consist of a characteristic doublet of quartets due to the H-12a proton in the region of 5.29–5.47 ppm with $^3J$=7.0 Hz and $^5J_{H,F}$=2.5 Hz (for **6a**: td, $^3J_{H,H}\approx{}^5J_{H,F}$=6.4 Hz, $^5J_{H,F}$=2.1 Hz) and a broad singlet due to the H-4a proton at 5.51–5.60 ppm (for **6a**: br d, $J$=2.0 Hz). In *exo*-isomers **6e,f**, the H-12a proton appeared as a quintet at 4.56–4.70 ppm with $J$=2.0 Hz, and H-4a occurred as a doublet at 5.41–5.44 ppm with $J$=2.4 Hz, that is, in the *endo*-isomers these protons are more deshielded than in the *exo*-isomers. Since a similar regularity is retained for *endo*- and *exo*-adducts **6g–k** and **7a–d,j–l**, it can be assumed that the chemical shifts of H-12a and H-4a (H-11a and H-3a for **7**) have diagnostic value in this series of compounds and, hence, the assignment of the signals in the $^1$H NMR spectra of fused pyrans *endo*-**3** and *exo*-**3**, as previously reported,[4] should be reversed. In the case of **6i–k**, integration of diagnostic signals due to H-12a and H-4a indicated that the *exo*-isomer was predominant.

To confirm the relative configuration of the H-12a, H-12b and H-4a atoms in *endo*-cycloadducts **6**, an X-ray diffraction study was carried out on crystals of **6a**. This study proved the *endo*-structure with the *cis*/*cis*-arrangement of the nodal hydrogen atoms in compounds **6** and **7** (Fig. 2, Table 3).

Next, taking into account the above results, it was of interest to evaluate the reactivity of chromones **5** with ethyl vinyl ether (10 equiv). In this case, the reaction was carried out without solvent at 80 °C for 10 h to give fused pyrans *endo*-**8a,b,e,j** in 53–72% yields as the sole products without formation of the *exo*-isomers (with the exception of **5j** from which only a small amount (2–3%) of *exo*-adduct **8j** could be detected by the $^1$H NMR spectroscopy). This result clearly demonstrates that the cycloaddition process proceeded with high regio- and stereoselectivity. The synthesis of the previously described *endo*-**8m**[3a,c,4] was undertaken for comparison of its qualitative $^1$H NMR spectrum to that of $R^F$-containing compounds **8** (Scheme 4).

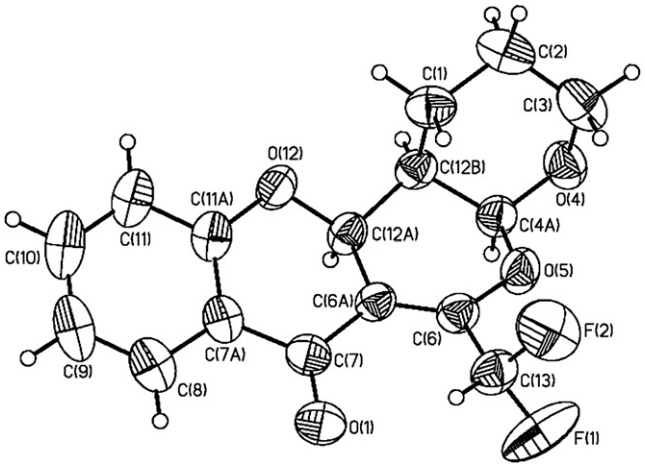
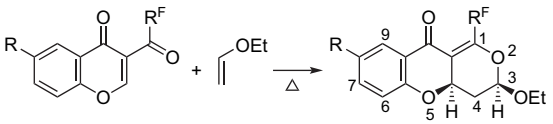



**Figure 2.** X-ray crystal structure of *endo*-cycloadduct **6a** (thermal ellipsoids at 50% probability).

**Table 3**
Selected bond lengths (Å) and bond angles (°) of compounds **6a** and **8e**

| **6a** | | **8e** | |
|---|---|---|---|
| Bond lengths | | | |
| O(5)–C(6) | 1.3460(13) | O(5)–C(5A) | 1.3579(14) |
| O(5)–C(4A) | 1.4669(14) | O(5)–C(4A) | 1.4446(14) |
| O(4)–C(4A) | 1.3787(14) | C(4A)–C(4) | 1.5077(18) |
| O(12)–C(11A) | 1.3601(14) | C(4A)–C(10A) | 1.5091(15) |
| O(12)–C(12A) | 1.4421(14) | O(2)–C(1) | 1.3384(16) |
| C(6A)–C(6) | 1.3389(15) | O(2)–C(3) | 1.4799(14) |
| C(6A)–C(7) | 1.4731(16) | O(3)–C(3) | 1.3621(16) |
| C(6A)–C(12A) | 1.5068(16) | C(10A)–C(1) | 1.3335(18) |
| C(12A)–C(12B) | 1.5148(16) | C(10A)–C(10) | 1.4763(18) |
| C(12B)–C(4A) | 1.5126(16) | O(1)–C(10) | 1.2245(14) |
| C(12B)–C(1) | 1.5257(18) | C(5A)–C(9A | 1.4000(16) |
| C(7)–O(1) | 1.2280(15) | C(9A)–C(10) | 1.4793(18) |
| C(7)–C(7A) | 1.4749(17) | C(4)–C(3) | 1.4913(17) |
| C(6)–C(13) | 1.5013(17) | C(1)–C(13) | 1.5145(17) |
| Bond angles | | | |
| C(6)–O(5)–C(4A) | 117.36(8) | C(5A)–O(5)–C(4A) | 115.26(8) |
| C(11A)–O(12)–C(12A) | 115.14(9) | O(5)–C(4A)–C(4) | 107.60(9) |
| C(6)–C(6A)–C(7) | 124.47(10) | O(5)–C(4A)–C(10A) | 110.24(9) |
| C(6)–C(6A)–C(12A) | 119.56(10) | C(4)–C(4A)–C(10A) | 111.68(10) |
| C(7)–C(6A)–C(12A) | 115.89(9) | C(1)–O(2)–C(3) | 114.05(9) |
| O(12)–C(12A)–C(6A) | 111.28(10) | C(1)–C(10A)–C(10) | 126.37(11) |
| O(12)–C(12A)–C(12B | 106.67(9) | C(1)–C(10A)–C(4A) | 119.84(11) |
| C(6A)–C(12A)–C(12B) | 111.81(9) | C(10)–C(10A)–C(4A) | 113.74(10) |
| C(4A)–C(12B)–C(12A) | 108.28(9) | O(5)–C(5A)–C(6) | 117.24(10) |
| C(4A)–C(12B)–C(1) | 110.37(11) | O(5)–C(5A)–C(9A) | 122.27(11) |
| O(1)–C(7)–C(6A) | 124.01(11) | O(1)–C(10)–C(10A) | 124.14(12) |
| O(1)–C(7)–C(7A) | 121.29(11) | O(1)–C(10)–C(9A) | 121.68(13) |
| C(6A)–C(6)–C(13) | 125.04(11) | C(10A)–C(1)–C(13) | 125.98(12) |
| O(5)–C(6)–C(13) | 110.03(10) | O(2)–C(1)–C(13) | 108.92(11) |

The structural assignment for compounds **8** was based on the two high field signals of the H-3 and H-4a protons in the $^1$H NMR spectra. The signal of H-3 appeared as a doublet of doublets at $\delta$ 5.23–5.36 ppm with large and small coupling constants ($^3J$=6.8–8.1 and 2.1–2.7 Hz) due to coupling with the axial and equatorial protons H-4. Thus, the hemiacetalic proton at C-3 obviously adopts a pseudo-axial position, and the ethoxy group occupies a pseudo-equatorial position. The methylene protons of this group appeared as a pair of double quartets at $\delta$ 3.7 and 4.0 ppm ($^2J$=9.7 Hz, $^3J$=7.1 Hz) due to the chiral centre. Another characteristic feature was the appearance of the signal of H-4a as a triplet of quartets at $\delta$ 5.08–5.15 ppm with $^3J$=7.0–7.5 Hz due to coupling with two protons at C-4 and $^5J_{H,F}$=2.2 Hz due to homoallylic coupling with the $CF_3$ group (tdd for **8a** and td for **8j**). In the $^1$H NMR spectrum of *endo*-**8m**, the signal of the H-3 proton appeared as a doublet of doublets at $\delta$ 5.21 ppm ($^3J$=10.0 and 2.1 Hz) and H-4a at 5.19 ppm (ddd, $^3J$=9.9, 6.7 Hz, $^4J$=1.4 Hz); large coupling constants, $^3J$=9.9–10.0 Hz, for **8m** revealed the axial/axial alignment of H-3 and H-4a. This means that the relative stereochemistry of these protons is cis. In the case of $R^F$-containing adducts **8**, a decrease in large coupling




**5** *endo*-**8**

| Chromone | $R^F$ | R | Adduct | Yield (%) |
|---|---|---|---|---|
| **5a** | $CF_2H$ | H | **8a** | 53 |
| **5b** | $CF_3$ | H | **8b** | 54 |
| **5e** | $CF_3$ | Cl | **8e** | 67 |
| **5j** | $(CF_2)_2H$ | H | **8j** | 72 |
| **5m** | H | H | **8m** | 74[a] |

**Scheme 4.**

constants compared to that of *endo*-**8m** can be a consequence of a distorted half-chair conformation due to steric repulsion between the bulky $R^F$ group and the carbonyl oxygen atom (see Table 3). Finally, the *endo*-structure with the cis-arrangement of the H-4a and H-3 hydrogen atoms in compounds **8** was confirmed by X-ray crystallographic analysis after the isolation of pyran **8e** as a single crystal from the reaction mixture (Fig. 3, Table 3). Note that the mass spectra of **6b**, **7b** and **8b** are identical and represent the mass spectrum of 3-(trifluoroacetyl)chromone **5b**.

Remarkable progress has been made in the development of new and efficient methods for synthesis of trifluoromethylated pyridines because of their potential ability as agrochemicals[11] and medicines.[7] 2,6-Diaryl-4-(trifluoromethyl)pyridines have recently been synthesized by the reaction of enamines, prepared from substituted acetophenones and morpholine, with trifluoromethylated β-diketones in the presence of ammonium acetate.[12a] The condensation of $CF_3$-containing α,β-unsaturated ketones, β-diketones and chromones with primary enamines, such as β-aminocrotononitrile and ethyl β-aminocrotonates, affords 2- and 4-(trifluoromethyl)pyridine.[12b–h] These compounds were also obtained from the reaction of trifluoromethylated α,β-unsaturated ketones and β-diketones with *N*-silyl-1-azaallyl anions[12i] by Hantzsch's dihydropyridine synthesis[12j] and Suzuki cross-coupling.[12k]

As mentioned above, 2-alkoxydihydropyrans can be considered as precursors for functionalized pyridine derivatives. In this context, we examined the possibility of preparing 2-$CF_3$-pyridines **9** from cycloadducts **6**, which may be regarded as 1,5-dicarbonyl compounds in protected form. After some optimization, it was found that $CF_3$-containing fused pyrans **6c**,**e**,**f** gave the required pyridines **9c**,**e**,**f** in 40–71% yields on reflux with ammonium acetate in ethanol for 7–8 h. This reaction represents a new route for the synthesis of trifluoromethylated pyridines possessing a 3-hydroxypropyl group, which are difficult to prepare by other methods. A possible reaction pathway is presented in the Scheme 5 and includes the acid-catalyzed nucleophilic 1,4-addition of ammonia, opening of two pyran cycles and heterocyclization to the pyridine system. This one-pot procedure is convenient and straightforward with simple product isolation, however, attempts to convert adducts **7** into the corresponding pyridines bearing a 2-hydroxyethyl group under the same reaction conditions gave only unidentified multicomponent mixtures from which no individual products could be isolated.

The structures of pyridines **9** compare well with the results of elemental analysis, $^1H$, $^{19}F$, $^{13}C$ NMR and IR spectroscopy. In the $^1H$ NMR spectra of **9c**,**e**,**f** the methylene protons of the side chain showed simple splitting, in contrast to the complex coupling observed for the ring protons in the starting materials. In addition,

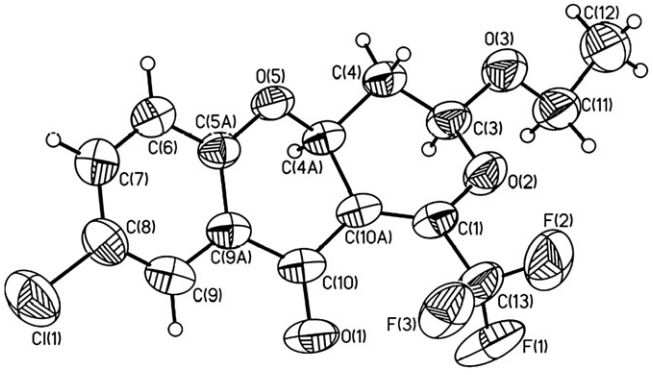
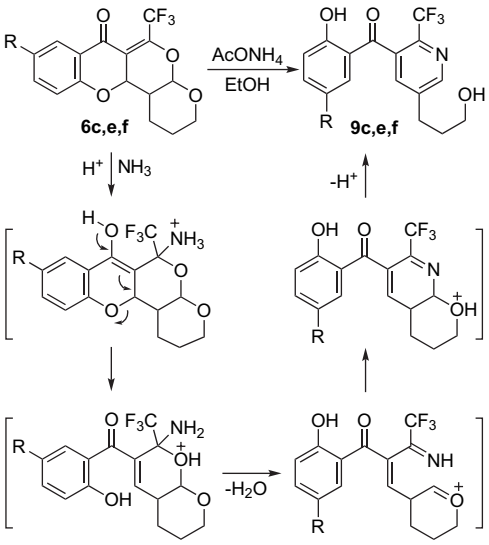



**Figure 3.** X-ray crystal structure of *endo*-cycloadduct **8e** (thermal ellipsoids at 50% probability).

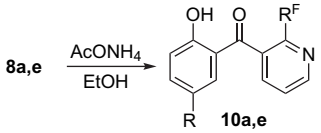



| Adduct | R | Pyridine | Yield (%) |
|---|---|---|---|
| **6c** | Me | **9c** | 71 |
| **6e** | Cl | **9e** | 67 |
| **6f** | $NO_2$ | **9f** | 40 |

**Scheme 5.**

another characteristic feature of the $^1H$ NMR spectra was the appearance of two doublets at $\delta$ 7.61–7.67 and 8.73–8.81 ppm due to the pyridine H-4 and H-6 protons ($^4J$=1.5–1.8 Hz), respectively. The presence of a hydroxyl proton involved in a hydrogen bond with the carbonyl group was identified by the resonance at $\delta$ 11.54–12.30 ppm. In the $^{19}F$ NMR spectra, $CF_3$ group of **9c**,**e** appeared as a singlet at 98.6 ppm ($C_6F_6$); the $^{13}C$ NMR spectrum of **9e** exhibits a quartet ($^1J_{C,F}$=275.2 Hz) at 121.2 ppm for the carbon of the $CF_3$ group and a quartet ($^2J_{C,F}$=35.0 Hz) at 142.3 ppm for the *C*–$CF_3$.

Analogous reaction of fused pyrans **8a**,**e** with ammonium acetate gave pyridines **10a**,**e**, which were fully characterized and their structures confirmed by spectroscopic techniques (Scheme 6). As far as we are aware, only one example of a similar transformation involving the cycloadduct of 3-formylchromone and ethyl vinyl ether (compound **8m**) resulting in 3-salicyloylpyridine has been published.[13] In the light of the present interest in fluoroaromatics as pharmaceutical intermediates,[7] this novel entry to fluorinated pyridines is noteworthy and will complement the published synthetic methods.[11,12] Taking into account that the salicyloyl substituent can easily be transformed via Dakin reaction into a carboxyl group,[14] this is also a method for preparing new $R^F$-containing derivatives of nicotinic acid with potential biological activity.




| Adduct | R | $R^F$ | Pyridine | Yield (%) |
|---|---|---|---|---|
| **8a** | H | $CF_2H$ | **10a** | 55 |
| **8e** | Cl | $CF_3$ | **10e** | 42 |

**Scheme 6.**

## 3. Conclusions

In conclusion, we have shown, for the first time, that the hetero-Diels–Alder reaction between 3-(polyfluoroacyl)chromones and enol ethers provides a short and stereoselective approach to the synthesis of a variety of $R^F$-containing fused pyrans, which can be considered as masked 1,5-dicarbonyl compounds and offer a new synthetic route to the preparation of 2-$R^F$-nicotinic acid derivatives. The latter are of interest as biologically active compounds and hardly obtainable by other methods.

## 4. Experimental

### 4.1. General

$^1$H (400 MHz), $^{13}$C (100 MHz) and $^{19}$F (376 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer in DMSO-$d_6$ with TMS and $C_6F_6$ as internal standards, respectively. IR spectra were recorded on a Perkin–Elmer Spectrum BX-II instrument as KBr discs. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. Melting points are uncorrected. All solvents used were dried and distilled as per standard procedures. The starting chromones **5a**–**m** were prepared according to described procedures.[6a,b,3c]

### 4.2. General procedure for the synthesis of fused pyrans (6a–k)

A solution of 3-$R^F$CO-chromone **5** (1.0 mmol) in 3,4-dihydro-2*H*-pyran (850 mg, 10.0 mmol) was refluxed for 4 h (for **5f** at ~20 °C for 2 days). After cooling, the resulting mixture was diluted with hexane (3 mL) and ether (0.5 mL). The solid product obtained at standing was collected by filtration, washed with hexane and dried to give compounds **6** as colourless crystals.

#### *4.2.1. 6-(Difluoromethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one (**6a**)*

Yield 52%, mp 216–217 °C; IR (KBr) 1662, 1619, 1604, 1468 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**6a** (100%) $\delta$ 1.56–2.16 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.57–2.64 (m, 1H, H-12b), 3.88 (ddt, 1H, 3-C*H*H, $^2J$=11.7 Hz, $^3J$=4.7 Hz, $^3J$=$^4J$=1.7 Hz), 4.04 (td, 1H, 3-CH*H*, $^2J$=$^3J$=11.7 Hz, $^3J$=3.2 Hz), 5.32 (td, 1H, H-12a, $^3J\approx{}^5J_{H,F}$=6.4 Hz, $^5J_{H,F}$=2.1 Hz), 5.58 (br d, 1H, H-4a, $^3J$=2.0 Hz), 6.95 (dd, 1H, H-11, $^3J$=8.4 Hz, $^4J$=0.9 Hz), 7.07 (ddd, 1H, H-9, $^3J$=7.9, 7.3 Hz, $^4J$=1.1 Hz), 7.36 (dd, 1H, $CF_2H$, $^2J_{H,F}$=52.6, 53.8 Hz), 7.49 (ddd, 1H, H-10, $^3J$=8.4, 7.2 Hz, $^4J$=1.8 Hz), 7.94 (dd, 1H, H-8, $^3J$=7.9 Hz, $^4J$=1.8 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ 34.59 (ddd, C*F*FH, $^2J_{F,F}$=324.4 Hz, $^2J_{F,H}$=53.8 Hz, $^5J_{F,H}$=2.1 Hz), 36.65 (ddd, CF*F*H, $^2J_{F,F}$=324.4 Hz, $^2J_{F,H}$=52.6 Hz, $^5J_{F,H}$=6.1 Hz). Anal. Calcd for $C_{16}H_{14}F_2O_4$: C, 62.34; H, 4.58. Found: C, 62.28; H, 4.50.

#### *4.2.2. 6-(Trifluoromethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one (**6b**)*

Yield 42%, mp 198–199 °C; IR (KBr) 1675, 1625, 1606, 1476, 1467 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**6b** (100%) $\delta$ 1.57–2.20 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.58–2.65 (m, 1H, H-12b), 3.90 (ddt, 1H, 3-C*H*H, $^2J$=11.6 Hz, $^3J$=4.6 Hz, $^3J$=$^4J$=1.7 Hz), 4.03 (td, 1H, 3-CH*H*, $^2J$=$^3J$=11.6 Hz, $^3J$=3.6 Hz), 5.34 (dq, 1H, H-12a, $^3J$=7.0 Hz, $^5J_{H,F}$=2.5 Hz), 5.54 (br s, 1H, H-4a), 6.95 (dd, 1H, H-11, $^3J$=8.3 Hz, $^4J$=0.9 Hz), 7.07 (ddd, 1H, H-9, $^3J$=7.9, 7.3 Hz, $^4J$=1.0 Hz), 7.48 (ddd, 1H, H-10, $^3J$=8.4, 7.3 Hz, $^4J$=1.7 Hz), 7.97 (dd, 1H, H-8, $^3J$=7.9 Hz, $^4J$=1.7 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 16.95, 22.94, 33.79, 61.65. 73.83, 98.53, 109.39 (d, C-6a, $^3J_{C,F}$=2.4 Hz), 117.64, 118.61 (q, $CF_3$, $^1J_{C,F}$=276.5 Hz), 121.14, 122.24, 126.89, 136.30, 145.81 (q, *C*–$CF_3$, $^2J_{C,F}$=38.3 Hz), 160.01, 178.31 (C=O); MS (EI): *m*/*z* (%) 242 $[M-C_5H_8O]^+$ (18), 173 $[M-C_5H_8O-CF_3]^+$ (100), 121 $[HOC_6H_4CO]^+$ (84), 69 $[CF_3]^+$ (23), 63 (30), 53 (63). Anal. Calcd for $C_{16}H_{13}F_3O_4$: C, 58.90; H, 4.02. Found: C, 58.68; H, 4.16.

#### *4.2.3. 9-Methyl-6-(trifluoromethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one (**6c**)*

Yield 51%, mp 208–209 °C; IR (KBr) 1685, 1634, 1615, 1582, 1492 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**6c** (100%) $\delta$ 1.57–2.20 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.32 (s, 3H, Me), 2.56–2.63 (m, 1H, H-12b), 3.89 (ddt, 1H, 3-C*H*H, $^2J$=11.6 Hz, $^3J$=4.6 Hz, $^4J$=1.7 Hz), 4.03 (td, 1H, 3-CH*H*, $^2J\approx{}^3J$=11.6 Hz, $^3J$=3.6 Hz), 5.29 (dq, 1H, H-12a, $^3J$=7.0 Hz, $^5J_{H,F}$=2.6 Hz), 5.52 (br s, 1H, H-4a), 6.84 (d, 1H, H-11, $^3J$=8.4 Hz), 7.29 (ddq, 1H, H-10, $^3J$=8.4 Hz, $^4J$=2.3, 0.6 Hz), 7.75 (dq, 1H, H-8, $^4J$=2.3, 0.5 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$, HFB) $\delta$ 94.87 (d, $CF_3$, $^5J_{F,H}$=2.6 Hz). Anal. Calcd for $C_{17}H_{15}F_3O_4$: C, 60.00; H, 4.44. Found: C, 59.99; H, 4.16.

#### *4.2.4. 10-Methoxy-6-(trifluoromethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6][4,3-b]chromen-7-one (**6d**)*

Yield 27%, mp 185–186 °C; IR (KBr) 1674, 1630, 1605, 1576, 1498 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**6d** (100%) $\delta$ 1.57–2.19 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.55–2.62 (m, 1H, H-12b), 3.84 (s, 3H, MeO), 3.89 (ddt, 1H, 3-C*H*H, $^2J$=11.6 Hz, $^3J$=4.9 Hz, $^3J$=$^4J$=1.7 Hz), 4.03 (td, 1H, 3-CH*H*, $^2J$=$^3J$=11.6 Hz, $^3J$=3.7 Hz), 5.31 (dq, 1H, H-12a, $^3J$=7.0 Hz, $^5J_{H,F}$=2.6 Hz), 5.51 (br s, 1H, H-4a), 6.40 (d, 1H, H-11, $^4J$=2.4 Hz), 6.63 (dd, 1H, H-9, $^3J$=8.9 Hz, $^4J$=2.4 Hz), 7.91 (d, 1H, H-8, $^3J$=8.9 Hz). Anal. Calcd for $C_{17}H_{15}F_3O_5$: C, 57.31; H, 4.24. Found: C, 56.91; H, 4.28.

#### *4.2.5. 9-Chloro-6-(trifluoromethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one (**6e**)*

Yield 73%, mp 201–202 °C; IR (KBr) 1684, 1662, 1627, 1602, 1473 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**6e** (97%) $\delta$ 1.57–2.19 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.58–2.65 (m, 1H, H-12b), 3.90 (ddt, 1H, 3-C*H*H, $^2J$=11.6 Hz, $^3J$=4.6 Hz, $^3J$=$^4J$=1.7 Hz), 4.02 (td, 1H, 3-CH*H*, $^2J$=$^3J$=11.6 Hz, $^3J$=3.6 Hz), 5.32 (dq, 1H, H-12a, $^3J$=7.0 Hz, $^5J_{H,F}$=2.5 Hz), 5.54 (br s, 1H, H-4a), 6.92 (d, 1H, H-11, $^3J$=8.8 Hz), 7.42 (dd, 1H, H-10, $^3J$=8.8 Hz, $^4J$=2.7 Hz), 7.91 (d, 1H, H-8, $^4J$=2.7 Hz); *exo*-**6e** (3%) $\delta$ 1.50–2.20 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.49–2.55 (m, 1H, H-12b), 3.84–4.03 (m, 2H, 3-$CH_2$), 4.56 (quint, 1H, H-12a, $^3J$=$^5J_{H,F}$=2.0 Hz), 5.41 (d, 1H, H-4a, $^3J$=2.4 Hz), 6.94 (d, 1H, H-11, $^3J$=8.8 Hz), 7.43 (dd, 1H, H-10, $^3J$=8.8 Hz, $^4J$=2.6 Hz), 7.94 (d, 1H, H-8, $^4J$=2.6 Hz). Anal. Calcd for $C_{16}H_{12}ClF_3O_4$: C, 53.28; H, 3.35. Found: C, 53.27; H, 3.32.

#### *4.2.6. 9-Nitro-6-(trifluoromethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one (**6f**)*

Yield 78%, mp 174–175 °C; IR (KBr) 1674, 1616, 1519, 1481, 1354 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**6f** (96%) $\delta$ 1.55–2.22 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.65–2.72 (m, 1H, H-12b), 3.93 (ddt, 1H, 3-C*H*H, $^2J$=11.6 Hz, $^3J$=4.8 Hz, $^3J$=$^4J$=1.7 Hz), 4.03 (td, 1H, 3-CH*H*, $^2J$=$^3J$=11.6 Hz, $^3J$=3.6 Hz), 5.47 (dq, 1H, H-12a, $^3J$=7.0 Hz, $^5J_{H,F}$=2.5 Hz), 5.60 (br s, 1H, H-4a), 7.10 (d, 1H, H-11, $^3J$=9.1 Hz), 8.34 (dd, 1H, H-10, $^3J$=9.1 Hz, $^4J$=2.8 Hz), 8.85 (d, 1H, H-8, $^4J$=2.8 Hz); *exo*-**6f** (4%) $\delta$ 1.55–2.22 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.57–2.64 (m, 1H, H-12b), 3.90–4.07 (m, 2H, 3-$CH_2$), 4.70 (quint, 1H, H-12a, $^3J$=$^5J_{H,F}$=2.0 Hz), 5.44 (d, 1H, H-4a, $^3J$=2.4 Hz), 7.13 (d, 1H, H-11, $^3J$=9.1 Hz), 8.35 (dd, 1H, H-10, $^3J$=9.1 Hz, $^4J$=2.8 Hz), 8.88 (d, 1H, H-8, $^4J$=2.8 Hz). Anal. Calcd for $C_{16}H_{12}F_3NO_6$: C, 51.76; H, 3.26; N, 3.77. Found: C, 51.79; H, 3.24; N, 3.74.

#### *4.2.7. 9,11-Dibromo-6-(trifluoromethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6][4,3-b]chromen-7-one (**6g**)*

Yield 63%, mp 177–178 °C; IR (KBr) 1700, 1684, 1630, 1587, 1449 cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-$d_6$) *endo*-**6g** (60%) $\delta$ 1.45–2.03 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.54–2.76 (m, 1H, H-12b), 3.75–3.90 (m, 2H, 3-$CH_2$), 5.70 (dq, 1H, H-12a, $^3J$=7.0 Hz, $^5J_{H,F}$=2.5 Hz), 5.82 (d, 1H,

H-4a, $^3J$=1.8 Hz), 7.89 (d, 1H, H-10, $^4J$=2.4 Hz), 8.17 (d, 1H, H-8, $^4J$=2.4 Hz); *exo*-**6g** (40%) δ 1.45–2.03 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.54–2.76 (m, 1H, H-12b), 3.75–3.90 (m, 2H, 3-$CH_2$), 5.20–5.24 (m, 1H, H-12a), 5.57 (d, 1H, H-4a, $^3J$=2.5 Hz), 7.92 (d, 1H, H-10, $^4J$=2.4 Hz), 8.18 (d, 1H, H-8, $^4J$=2.4 Hz). Anal. Calcd for $C_{16}H_{11}Br_2F_3O_4$: C, 39.70; H, 2.29. Found: C, 39.58; H, 2.24.

#### 4.2.8. 9-Nitro-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one (**6h**)

Yield 62%, mp 195–196 °C; IR (KBr) 1680, 1608, 1521, 1471, 1438, 1345, 1333 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *endo*-**6h** (55%) δ 1.56–2.12 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.58–2.65 (m, 1H, H-12b), 3.88 (ddt, 1H, 3-C*H*H, $^2J$=11.6 Hz, $^3J$=4.9 Hz, $^3J$=$^4J$=1.6 Hz), 3.96 (td, 1H, 3-CH*H*, $^2J$=$^3J$=11.6 Hz, $^3J$=3.1 Hz), 5.44 (dd, 1H, H-12a, $^3J$=6.5 Hz, $^4J$=1.7 Hz), 5.55 (br d, 1H, H-4a, *J*=1.7 Hz), 7.06 (d, 1H, H-11, $^3J$=9.1 Hz), 7.74 (d, 1H, H-6, *J*=1.7 Hz), 8.30 (dd, 1H, H-10, $^3J$=9.1 Hz, $^4J$=2.8 Hz), 8.82 (d, 1H, H-8, $^4J$=2.8 Hz); *exo*-**6h** (45%) δ 1.56–2.12 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.47–2.53 (m, 1H, H-12b), 3.75–3.82 (m, 1H, 3-C*H*H), 4.03–4.09 (m, 1H, 3-CH*H*), 4.95 (dd, 1H, H-12a, $^3J$=6.0, $^4J$=1.5 Hz), 5.24 (d, 1H, H-4a, $^3J$=2.7 Hz), 7.10 (d, 1H, H-11, $^3J$=9.1 Hz), 7.63 (d, 1H, H-6, $^4J$=1.5 Hz), 8.31 (dd, 1H, H-10, $^3J$=9.1 Hz, $^4J$=2.8 Hz), 8.86 (d, 1H, H-8, $^4J$=2.8 Hz). Anal. Calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.34; H, 4.34; N, 4.57.

#### 4.2.9. 9,11-Dibromo-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one (**6i**)

Yield 35%, mp 217–218 °C; IR (KBr) 1670, 1604, 1584, 1447, 1431 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$) *endo*-**6i** (10%) δ 1.50–2.00 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.40–2.60 (m, 1H, H-12b), 3.65–3.95 (m, 2H, 3-$CH_2$), 5.55 (dd, 1H, H-12a, $^3J$=6.7 Hz, $^4J$=1.7 Hz), 5.66 (br d, 1H, H-4a, $^3J$=1.7 Hz), 7.75 (d, 1H, H-6, $^4J$=1.7 Hz), 7.84 (d, 1H, H-10, $^4J$=2.5 Hz), 8.10 (d, 1H, H-8, $^4J$=2.5 Hz); *exo*-**6i** (90%) δ 1.50–2.00 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.40–2.60 (m, 1H, H-12b), 3.65–3.95 (m, 2H, 3-$CH_2$), 5.19 (dd, 1H, H-12a, $^3J$=7.3 Hz, $^4J$=1.5 Hz), 5.32 (d, 1H, H-4a, $^3J$=2.7 Hz), 7.67 (d, 1H, H-6, $^4J$=1.5 Hz), 7.86 (d, 1H, H-10, $^4J$=2.5 Hz), 8.11 (d, 1H, H-8, $^4J$=2.5 Hz). Anal. Calcd for $C_{15}H_{12}Br_2O_4$: C, 43.30; H, 2.91. Found: C, 43.30; H, 2.96.

#### 4.2.10. 6-(1,1,2,2-Tetrafluoroethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6]pyrano[4,3-b]chromen-7-one (**6j**)

This compound was prepared according to procedure described in Section 4.3. Yield 56%, mp 142–144 °C; IR (KBr) 1679, 1622, 1604, 1576, 1467 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *endo*-**6j** (47%) δ 1.60–2.20 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.57–2.64 (m, 1H, H-12b), 3.82–4.07 (m, 2H, 3-$CH_2$), 5.33 (dd, 1H, H-12a, $^3J$=7.1 Hz, $^5J_{H,F}$=4.6 Hz), 5.51 (br s, 1H, H-4a), 6.79 (tdd, 1H, $CF_2CF_2H$, $^2J_{H,F}$=53.5 Hz, $^3J_{H,F}$=11.0, 0.5 Hz), 6.95 (dd, 1H, H-11, $^3J$=8.4 Hz, $^4J$=0.8 Hz), 7.07 (ddd, 1H, H-9, $^3J$=7.9, 7.3 Hz, $^4J$=1.1 Hz), 7.49 (ddd, 1H, H-10, $^3J$=8.3, 7.2 Hz, $^4J$=1.7 Hz), 7.92 (dd, 1H, H-8, $^3J$=7.9 Hz, $^4J$=1.7 Hz); *exo*-**6j** (53%) δ 1.50–2.20 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.49–2.55 (m, 1H, H-12b), 3.82–4.07 (m, 2H, 3-$CH_2$), 4.54–4.56 (m, 1H, H-12a), 5.41 (d, 1H, H-4a, $^3J$=2.6 Hz), 6.79 (tdd, 1H, $CF_2CF_2H$, $^2J_{H,F}$=53.5 Hz, $^3J_{H,F}$=10.5, 1.0 Hz), 6.99 (dd, 1H, H-11, $^3J$=8.4 Hz, $^4J$=0.8 Hz), 7.09 (ddd, 1H, H-9, $^3J$=7.9, 7.3 Hz, $^4J$=1.1 Hz), 7.51 (ddd, 1H, H-10, $^3J$=8.4, 7.2 Hz, $^4J$=1.7 Hz), 7.96 (dd, 1H, H-8, $^3J$=7.9 Hz, $^4J$=1.7 Hz). Anal. Calcd for $C_{17}H_{14}F_4O_4$: C, 56.99; H, 3.94. Found: C, 57.10; H, 3.76.

#### 4.2.11. 9-Methyl-6-(1,1,2,2-tetrafluoroethyl)-2,3,12a,12b-tetrahydro-1H,4aH,7H-pyrano[3′,2′:5,6][4,3-b]chromen-7-one (**6k**)

This compound was prepared according to procedure described in Section 4.3. Yield 31%, mp 128–130 °C; IR (KBr) 1675, 1622, 1580, 1488 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *endo*-**6k** (47%) δ 1.60–2.20 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.32 (s, 3H, Me), 2.55–2.62 (m, 1H, H-12b), 3.81–4.07 (m, 2H, 3-$CH_2$), 5.28 (dd, 1H, H-12a, $^3J$=7.0 Hz, $^5J_{H,F}$=4.6 Hz), 5.49 (br s, 1H, H-4a), 6.79 (tdd, 1H, $CF_2CF_2H$, $^2J_{H,F}$=53.5 Hz, $^3J_{H,F}$=11.0, 0.5 Hz), 6.85 (d, 1H, H-11, $^3J$=8.4 Hz), 7.30 (dd, 1H, H-10, $^3J$=8.4 Hz, $^4J$=2.3 Hz), 7.71 (br d, 1H, H-8, $^4J$=2.0 Hz); *exo*-**6k** (53%) δ 1.50–2.20 (m, 4H, 1-$CH_2$, 2-$CH_2$), 2.33 (s, 3H, Me), 2.46–2.52 (m, 1H, H-12b), 3.81–4.07 (m, 2H, 3-$CH_2$), 4.50–4.52 (m, 1H, H-12a), 5.40 (d, 1H, H-4a, $^3J$=2.5 Hz), 6.79 (tdd, 1H, $CF_2CF_2H$, $^2J_{H,F}$=53.5 Hz, $^3J_{H,F}$=10.5, 1.0 Hz), 6.88 (d, 1H, H-11, $^3J$=8.4 Hz), 7.32 (dd, 1H, H-10, $^3J$=8.4 Hz, $^4J$=2.3 Hz), 7.74 (br d, 1H, H-8, $^4J$=2.0 Hz). Anal. Calcd for $C_{18}H_{16}F_4O_4$: C, 58.07; H, 4.33. Found: C, 58.06; H, 4.03.

### 4.3. General procedure for the synthesis of fused pyrans (7a–d,j–l)

A mixture of 3-$R^F$CO-chromone **5** (1.0 mmol) and 2,3-dihydrofuran (150 mg, 2.0 mmol) was heated at 60 °C for 4 h and additionally at 80 °C for 10 min. After cooling, the resulting mixture was diluted with hexane (3 mL) and ether (0.5 mL). The solid product obtained at standing was collected by filtration, washed with hexane and dried to give compounds **7** as colourless crystals.

#### 4.3.1. 5-(Difluoromethyl)-1,2,11a,11b-tetrahydro-3aH,6H-furo[3′,2′:5,6]pyrano[4,3-b]chromen-6-one (**7a**)

Yield 51%, mp 180–182 °C; IR (KBr) 1666, 1622, 1603, 1475, 1466 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *endo*-**7a** (97%) δ 2.15 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.5 Hz, $^3J$=9.6 Hz), 2.38 (dtd, 1H, 1-CH*H*, $^2J$=12.9 Hz, $^3J$=7.7, 2.7 Hz), 3.05 (dddd, 1H, H-11b, $^3J$=12.0, 8.2, 6.7, 3.8 Hz), 4.14 (ddd, 1H, 2-C*H*H, $^2J$=9.4, $^3J$=8.7, 7.5 Hz), 4.33 (ddd, 1H, 2-CH*H*, $^2J$=9.6, $^3J$=8.7, 2.7 Hz), 5.51 (ddd, 1H, H-11a, $^3J$=6.6 Hz, $^5J_{H,F}$=5.8, 2.6 Hz), 5.85 (d, 1H, H-3a, $^3J$=3.8 Hz), 6.97 (dd, 1H, H-10, $^3J$=8.4 Hz, $^4J$=1.0 Hz), 7.09 (ddd, 1H, H-8, $^3J$=8.0, 7.2 Hz, $^4J$=1.0 Hz), 7.36 (dd, 1H, $CF_2H$, $^2J_{H,F}$=52.8, 53.7 Hz), 7.50 (ddd, 1H, H-9, $^3J$=8.4, 7.2 Hz, $^4J$=1.7 Hz), 7.95 (dd, 1H, H-7, $^3J$=7.9 Hz, $^4J$=1.7 Hz); *exo*-**7a** (3%) δ 1.75–1.85 (m, 1H, 1-C*H*H), 2.30–2.38 (m, 1H, 1-CH*H*), 2.92–3.00 (m, 1H, H-11b), 4.08–4.15 (m, 1H, 2-C*H*H), 4.26–4.30 (m, 1H, 2-CH*H*), 4.85 (br d, 1H, H-11a, $^3J$=5.5 Hz), 5.55 (d, 1H, H-3a, $^3J$=3.7 Hz), 7.00 (dd, 1H, H-10, $^3J$=8.4 Hz, $^4J$=1.0 Hz), 7.11 (ddd, 1H, H-8, $^3J$=7.9, 7.2 Hz, $^4J$=1.0 Hz), 7.34 (t, 1H, $CF_2H$, $^2J_{H,F}$=53.0), 7.52 (ddd, 1H, H-9, $^3J$=8.4, 7.2 Hz, $^4J$=1.7 Hz), 7.99 (dd, 1H, H-7, $^3J$=7.9 Hz, $^4J$=1.7 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 23.30, 40.47, 68.44. 71.80, 103.20, 107.24 (dd, C-5a, $^3J_{C,F}$=6.1, 4.3 Hz), 108.08 (t, $CF_2H$, $^1J_{C,F}$=239.3 Hz), 117.61, 121.81, 122.21, 127.06, 136.20, 152.01 (t, *C*–$CF_3$, $^2J_{C,F}$=21.8 Hz), 160.12, 180.02 (C=O). Anal. Calcd for $C_{15}H_{12}F_2O_4$: C, 61.23; H, 4.11. Found: C, 61.13; H, 4.31.

#### 4.3.2. 5-(Trifluoromethyl)-1,2,11a,11b-tetrahydro-3aH,6H-furo[3′,2′:5,6]pyrano[4,3-b]chromen-6-one (**7b**)

Yield 69%, mp 143–144 °C; IR (KBr) 1679, 1636, 1605, 1576, 1466 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *endo*-**7b** (70%) δ 2.18 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.6 Hz, $^3J$=9.8 Hz), 2.42 (dtd, 1H, 1-CH*H*, $^2J$=12.9 Hz, $^3J$=7.6, 2.5 Hz), 2.99–3.07 (m, 1H, H-11b), 4.12–4.19 (m, 1H, 2-C*H*H), 4.36 (ddd, 1H, 2-CH*H*, $^2J$=9.6 Hz, $^3J$=8.6, 2.4 Hz), 5.52 (dq, 1H, H-11a, $^3J$=7.3 Hz, $^5J_{H,F}$=2.5 Hz), 5.79 (d, 1H, H-3a, $^3J$=3.5 Hz), 6.97 (dd, 1H, H-10, $^3J$=8.4 Hz, $^4J$=1.0 Hz), 7.09 (ddd, 1H, H-8, $^3J$=7.9, 7.2 Hz, $^4J$=1.0 Hz), 7.49 (ddd, 1H, H-9, $^3J$=8.4, 7.2 Hz, $^4J$=1.7 Hz), 7.98 (dd, 1H, H-7, $^3J$=7.9 Hz, $^4J$=1.7 Hz); *exo*-**7b** (30%) δ 1.78 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.6 Hz, $^3J$=9.8 Hz), 2.30–2.38 (m, 1H, 1-CH*H*), 2.92–2.99 (m, 1H, H-11b), 4.09–4.16 (m, 1H, 2-C*H*H), 4.29 (td, 1H, 2-CH*H*, $^2J$=$^3J$=9.2 Hz, $^3J$=2.4 Hz), 4.89 (br s, 1H, H-11a), 5.60 (d, 1H, H-3a, $^3J$=3.7 Hz), 6.99 (dd, 1H, H-10, $^3J$=8.4 Hz, $^4J$=1.0 Hz), 7.11 (ddd, 1H, H-8, $^3J$=7.9, 7.2 Hz, $^4J$=1.0 Hz), 7.51 (ddd, 1H, H-9, $^3J$=8.4, 7.2 Hz, $^4J$=1.7 Hz), 8.00 (dd, 1H, H-7, $^3J$=7.9 Hz, $^4J$=1.7 Hz); MS (EI): *m*/*z* (%) 242 $[M-C_4H_6O]^+$ (16), 173 $[M-C_4H_6O-CF_3]^+$ (100), 121 $[HOC_6H_4CO]^+$ (90), 69 $[CF_3]^+$ (21), 63 (30), 53 (64). Anal. Calcd for $C_{15}H_{11}F_3O_4$: C, 57.70; H, 3.55. Found: C, 57.87; H, 3.32.

#### 4.3.3. 8-Methyl-5-(trifluoromethyl)-1,2,11a,11b-tetrahydro-3aH,6H-furo[3′,2′:5,6]pyrano[4,3-b]chromen-6-one (**7c**)

Yield 68%, mp 147–149 °C; IR (KBr) 1683, 1639, 1615, 1576, 1488 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) *endo*-**7c** (69%) δ 2.11–2.23

(m, 1H, 1-C*H*H), 2.32 (s, 3H, Me), 2.36–2.45 (m, 1H, 1-CH*H*), 2.97–3.05 (m, 1H, H-11b), 4.09–4.18 (m, 1H, 2-C*H*H), 4.35 (ddd, 1H, 2-CH*H*, $^2J$=9.6 Hz, $^3J$=8.6, 2.4 Hz), 5.47 (dq, 1H, H-11a, $^3J$=7.3 Hz, $^5J_{H,F}$=2.6 Hz), 5.77 (d, 1H, H-3a, $^3J$=3.5 Hz), 6.86 (d, 1H, H-10, $^3J$=8.4 Hz), 7.28–7.33 (m, 1H, H-9), 7.76 (br d, 1H, H-7, $^4J$=1.8 Hz); *exo*-**7c** (31%) $\delta$ 1.71–1.83 (m, 1H, 1-C*H*H), 2.28–2.36 (m, 1H, 1-CH*H*), 2.33 (s, 3H, Me), 2.89–2.96 (m, 1H, H-11b), 4.08–4.15 (m, 1H, 2-C*H*H), 4.28 (td, 1H, 2-CH*H*, $^2J$=$^3J$=9.2 Hz, $^3J$=2.5 Hz), 4.84 (br s, 1H, H-11a), 5.59 (d, 1H, H-3a, $^3J$=3.7 Hz), 6.89 (d, 1H, H-10, $^3J$=8.4 Hz), 7.28–7.33 (m, 1H, H-9), 7.78 (br d, 1H, H-7, $^4J$=1.8 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$) *endo*-**7c** (67%) $\delta$ 95.14 (d, $CF_3$, $^5J_{F,H}$=2.6 Hz); *exo*-**7c** (33%) $\delta$ 95.80 (d, $CF_3$, $^5J_{F,H}$=2.0 Hz). Anal. Calcd for $C_{16}H_{13}F_3O_4$: C, 58.90; H, 4.02. Found: C, 58.68; H, 3.96.

#### *4.3.4. 9-Methoxy-5-(trifluoromethyl)-1,2,11a,11b-tetrahydro-3aH,6H-furo[3′,2′:5,6]pyrano[4,3-b]chromen-6-one (**7d**)*

Yield 53%, mp 155–157 °C; IR (KBr) 1676, 1622, 1571, 1491, 1463, 1447 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**7d** (93%) $\delta$ 2.17 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.6 Hz, $^3J$=9.6 Hz), 2.39 (dtd, 1H, 1-CH*H*, $^2J$=12.8 Hz, $^3J$=7.6, 2.5 Hz), 3.00 (dtd, 1H, H-11b, $^3J$=12.0, 7.8, 3.6 Hz), 3.85 (s, 3H, MeO), 4.14 (ddd, 1H, 2-C*H*H, $^2J$=9.5 Hz, $^3J$=8.6, 7.4 Hz), 4.35 (ddd, 1H, 2-CH*H*, $^2J$=9.6, $^3J$=8.7, 2.4 Hz), 5.50 (dq, 1H, H-11a, $^3J$=7.3 Hz, $^5J_{H,F}$=2.5 Hz), 5.77 (d, 1H, H-3a, $^3J$=3.6 Hz), 6.41 (d, 1H, H-10, $^4J$=2.4 Hz), 6.65 (dd, 1H, H-8, $^3J$=8.9 Hz, $^4J$=2.4 Hz), 7.92 (d, 1H, H-7, $^3J$=8.9 Hz); *exo*-**7d** (7%) $\delta$ 1.70–1.82 (m, 1H, 1-C*H*H), 2.86–2.94 (m, 1H, H-11b), 3.94 (s, 3H, MeO), 4.07–4.15 (m, 1H, 2-C*H*H), 4.24–4.30 (m, 1H, 2-CH*H*), 4.87 (br s, 1H, H-11a), 5.57 (d, 1H, H-3a, $^3J$=3.5 Hz), 6.43 (d, 1H, H-10, $^4J$=2.4 Hz), 6.66 (dd, 1H, H-8, $^3J$=8.9, $^4J$=2.4 Hz), 7.93 (d, 1H, H-7, $^3J$=8.9 Hz). Anal. Calcd for $C_{16}H_{13}F_3O_5$: C, 56.15; H, 3.83. Found: C, 56.25; H, 3.70.

#### *4.3.5. 5-(1,1,2,2-Tetrafluoroethyl)-1,2,11a,11b-tetrahydro-3aH,6H-furo[3′,2′:5,6]pyrano[4,3-b]chromen-6-one (**7j**)*

Yield 36%, mp 115–116 °C; IR (KBr) 1681, 1631, 1607, 1578, 1475, 1466 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**7j** (60%) $\delta$ 2.19 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.5 Hz, $^3J$=9.7 Hz), 2.41 (dtd, 1H, 1-CH*H*, $^2J$=12.9 Hz, $^3J$=7.6, 2.5 Hz), 3.02 (dtd, 1H, H-11b, $^3J$=11.9, 7.9, 3.6 Hz), 4.12–4.18 (m, 1H, 2-C*H*H), 4.35 (ddd, 1H, 2-CH*H*, $^2J$=9.6 Hz, $^3J$=8.6, 2.5 Hz), 5.51 (dd, 1H, H-11a, $^3J$=7.3 Hz, $^5J_{H,F}$=4.4 Hz), 5.76 (d, 1H, H-3a, $^3J$=3.5 Hz), 6.79 (tdd, 1H, $CF_2CF_2H$, $^2J_{H,F}$=53.8 Hz, $^3J_{H,F}$=10.5, 0.6 Hz), 6.97 (dd, 1H, H-10, $^3J$=8.4 Hz, $^4J$=1.0 Hz), 7.09 (ddd, 1H, H-8, $^3J$=7.9, 7.2 Hz, $^4J$=1.0 Hz), 7.50 (ddd, 1H, H-9, $^3J$=8.4, 7.2 Hz, $^4J$=1.7 Hz), 7.94 (dd, 1H, H-7, $^3J$=7.9 Hz, $^4J$=1.7 Hz); *exo*-**7j** (40%) $\delta$ 1.72 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.5 Hz, $^3J$=9.6 Hz), 2.33 (dddd, 1H, 1-CH*H*, $^2J$=12.2 Hz, $^3J$=8.4, 7.4, 2.5 Hz), 2.95 (dddd, 1H, H-11b, $^3J$=12.9, 8.4, 3.7, 1.0 Hz), 4.08–4.14 (m, 1H, 2-C*H*H), 4.27 (ddd, 1H, 2-CH*H*, $^2J$=9.5 Hz, $^3J$=8.5, 2.5 Hz), 4.86 (d, 1H, H-11a, $^3J$=3.9 Hz), 5.59 (d, 1H, H-3a, $^3J$=3.7 Hz), 6.76 (tdd, 1H, $CF_2CF_2H$, $^2J_{H,F}$=53.6 Hz, $^3J_{H,F}$=10.5, 1.1 Hz), 7.00 (dd, 1H, H-10, $^3J$=8.4 Hz, $^4J$=1.0 Hz), 7.11 (ddd, 1H, H-8, $^3J$=7.9, 7.2 Hz, $^4J$=1.0 Hz), 7.52 (ddd, 1H, H-9, $^3J$=8.4, 7.2 Hz, $^4J$=1.7 Hz), 7.96 (dd, 1H, H-7, $^3J$=7.9 Hz, $^4J$=1.7 Hz). Anal. Calcd for $C_{16}H_{12}F_4O_4$: C, 55.82; H, 3.51. Found: C, 55.49; H, 3.54.

#### *4.3.6. 8-Methyl-5-(1,1,2,2-tetrafluoroethyl)-1,2,11a,11b-tetrahydro-3aH,6H-furo[3′,2′:5,6]pyrano[4,3-b]chromen-6-one (**7k**)*

Yield 63%, mp 124–125 °C; IR (KBr) 1677, 1623, 1578, 1489, 1458 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**7k** (54%) $\delta$ 2.17 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.4 Hz, $^3J$=9.7 Hz), 2.32 (s, 3H, Me), 2.40 (dtd, 1H, 1-CH*H*, $^2J$=12.9 Hz, $^3J$=7.6, 2.6 Hz), 3.01 (dtd, 1H, H-11b, $^3J$=11.9, 7.9, 3.6 Hz), 4.11–4.17 (m, 1H, 2-C*H*H), 4.34 (ddd, 1H, 2-CH*H*, $^2J$=9.6 Hz, $^3J$=8.6, 2.5 Hz), 5.48 (dd, 1H, H-11a, $^3J$=7.3 Hz, $^5J_{H,F}$=4.6 Hz), 5.76 (d, 1H, H-3a, $^3J$=3.5 Hz), 6.79 (tdd, 1H, $CF_2CF_2H$, $^2J_{H,F}$=53.8 Hz, $^3J_{H,F}$=10.5, 0.5 Hz), 6.87 (d, 1H, H-10, $^3J$=8.5 Hz), 7.31 (dd, 1H, H-9, $^3J$=8.5 Hz, $^4J$=2.1 Hz), 7.71 (br d, 1H, H-7, $^4J$=1.8 Hz); *exo*-**7k** (46%) $\delta$ 1.72 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.5 Hz, $^3J$=9.6 Hz), 2.29–2.38 (m, 1H, 1-CH*H*), 2.33 (s, 3H, Me), 2.93 (dddd, 1H, H-11b, $^3J$=12.8, 8.5, 3.7, 0.5 Hz), 4.07–4.13 (m, 1H, 2-C*H*H), 4.26 (td, 1H, 2-CH*H*, $^2J$=$^3J$=9.0 Hz, $^3J$=2.5 Hz), 4.83 (d, 1H, H-11a, $^3J$=3.8 Hz), 5.58 (d, 1H, H-3a, $^3J$=3.6 Hz), 6.76 (tdd, 1H, $CF_2CF_2H$, $^2J_{H,F}$=53.6 Hz, $^3J_{H,F}$=10.5, 0.5 Hz), 6.90 (d, 1H, H-10, $^3J$=8.5 Hz), 7.33 (dd, 1H, H-9, $^3J$=8.5 Hz, $^4J$=2.1 Hz), 7.73 (br d, 1H, H-7, $^4J$=1.8 Hz). Anal. Calcd for $C_{17}H_{14}F_4O_4$: C, 56.99; H, 3.94. Found: C, 57.18; H, 3.78.

#### *4.3.7. 7,9-Dimethyl-5-(trifluoromethyl)-1,2,11a,11b-tetrahydro-3aH,6H-furo[3′,2′:5,6]pyrano[4,3-b]chromen-6-one (**7l**)*

Yield 26%, mp 154–155 °C; IR (KBr) 1679, 1621, 1564, 1474, 1460 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) *endo*-**7l** (93%) $\delta$ 2.15 (tt, 1H, 1-C*H*H, $^2J$=$^3J$=12.4 Hz, $^3J$=9.7 Hz), 2.31 (s, 3H, Me), 2.37 (dtd, 1H, 1-CH*H*, $^2J$=12.8 Hz, $^3J$=7.6, 2.5 Hz), 2.64 (s, 3H, Me), 2.98 (dtd, 1H, H-11b, $^3J$=12.0, 7.9, 3.8 Hz), 4.13 (ddd, 1H, 2-C*H*H, $^2J$=9.4, $^3J$=8.6, 7.5 Hz), 4.33 (ddd, 1H, 2-CH*H*, $^2J$=9.6 Hz, $^3J$=8.6, 2.4 Hz), 5.40 (dq, 1H, H-11a, $^3J$=7.3 Hz, $^5J_{H,F}$=2.5 Hz), 5.74 (d, 1H, H-3a, $^3J$=3.6 Hz), 6.65 (s, 1H, H-10), 6.69 (s, 1H, H-8); *exo*-**7l** (7%) $\delta$ 1.71–1.81 (m, 1H, 1-C*H*H), 2.31 (s, 3H, Me), 2.30–2.40 (m, 1H, 1-CH*H*), 2.65 (s, 3H, Me), 4.80 (br s, 1H, H-11a), 5.56 (d, 1H, H-3a, $^3J$=3.7 Hz), 6.65 (s, 1H, H-10), 6.69 (s, 1H, H-8). Anal. Calcd for $C_{17}H_{15}F_3O_4$: C, 60.00; H, 4.44. Found: C, 59.65; H, 4.23.

### 4.4. General procedure for the synthesis of fused pyrans (8a,b,e,j)

A solution of 3-$R^F$CO-chromone **5** (1.0 mmol) in ethyl vinyl ether (720 mg, 10.0 mmol) was heated at 80 °C for 10 h in a sealed tube. After cooling, the resulting mixture was diluted with hexane (3 mL) and ether (0.5 mL). The solid product obtained at standing was collected by filtration, washed with hexane and dried to give compounds **8** as colourless crystals.

#### *4.4.1. 1-(Difluoromethyl)-3-ethoxy-4,4a-dihydro-3H,10H-pyrano[4,3-b]chromen-10-one (**8a**)*

Yield 53%, mp 144–145 °C; IR (KBr) 1673, 1624, 1607, 1465 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.28 (t, 3H, Me, $J$=7.1 Hz), 2.48 (dt, 1H, C*H*H, $^2J$=14.2 Hz, $^3J$=6.8 Hz), 2.58 (ddd, 1H, CH*H*, $^2J$=14.2 Hz, $^3J$=7.1, 2.7 Hz), 3.72 (dq, 1H, OC*H*H, $^2J$=9.7 Hz, $^3J$=7.1 Hz), 4.02 (dq, 1H, OCH*H*, $^2J$=9.7 Hz, $^3J$=7.1 Hz), 5.08 (tdd, 1H, H-4a, $^3J$=7.0 Hz, $^5J_{H,F}$=4.6, 3.0 Hz), 5.36 (dd, 1H, H-3, $^3J$=6.8, 2.7 Hz), 6.99 (dd, 1H, H-6, $^3J$=8.4 Hz, $^4J$=1.0 Hz), 7.08 (ddd, 1H, H-8, $^3J$=7.9, 7.2 Hz, $^4J$=1.0 Hz), 7.24 (dd, 1H, $CF_2H$, $^2J_{H,F}$=53.0, 53.4 Hz), 7.49 (ddd, 1H, H-7, $^3J$=8.4, 7.2 Hz, $^4J$=1.8 Hz), 7.96 (dd, 1H, H-9, $^3J$=7.9 Hz, $^4J$=1.8 Hz). Anal. Calcd for $C_{15}H_{14}F_2O_4$: C, 60.81; H, 4.76. Found: C, 60.40; H, 4.52.

#### *4.4.2. 3-Ethoxy-1-(trifluoromethyl)-4,4a-dihydro-3H,10H-pyrano[4,3-b]chromen-10-one (**8b**)*

Yield 54%, mp 133–134 °C; IR (KBr) 1681, 1631, 1606, 1581, 1474, 1465 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.29 (t, 3H, Me, $J$=7.1 Hz), 2.46 (dt, 1H, C*H*H, $^2J$=14.0 Hz, $^3J$=7.6 Hz), 2.59 (ddd, 1H, CH*H*, $^2J$=14.0 Hz, $^3J$=7.4, 2.4 Hz), 3.72 (dq, 1H, OC*H*H, $^2J$=9.7 Hz, $^3J$=7.1 Hz), 4.00 (dq, 1H, OCH*H*, $^2J$=9.7 Hz, $^3J$=7.1 Hz), 5.15 (tq, 1H, H-4a, $^3J$=7.4 Hz, $^5J_{H,F}$=2.2 Hz), 5.30 (dd, 1H, H-3, $^3J$=7.8, 2.4 Hz), 6.98 (dd, 1H, H-6, $^3J$=8.4 Hz, $^4J$=1.0 Hz), 7.07 (ddd, 1H, H-8, $^3J$=7.9, 7.2 Hz, $^4J$=1.0 Hz), 7.48 (ddd, 1H, H-7, $^3J$=8.4, 7.2 Hz, $^4J$=1.7 Hz), 7.98 (dd, 1H, H-9, $^3J$=7.9 Hz, $^4J$=1.7 Hz); MS (EI): *m*/*z* (%) 242 $[M-C_4H_8O]^+$ (21), 173 $[M-C_4H_8O-CF_3]^+$ (100), 121 $[HOC_6H_4CO]^+$ (96), 69 $[CF_3]^+$ (26), 63 (33), 53 (72). Anal. Calcd for $C_{15}H_{13}F_3O_4$: C, 57.33; H, 4.17. Found: C, 57.34; H, 4.04.

#### *4.4.3. 8-Chloro-3-ethoxy-1-(trifluoromethyl)-4,4a-dihydro-3H,10H-pyrano[4,3-b]chromen-10-one (**8e**)*

Yield 67%, mp 160–162 °C; IR (KBr) 1679, 1633, 1602, 1472 $cm^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.29 (t, 3H, Me, $J$=7.1 Hz), 2.46 (dt, 1H, C*H*H, $^2J$=14.1 Hz, $^3J$=7.4 Hz), 2.59 (ddd, 1H, CH*H*, $^2J$=14.1 Hz, $^3J$=7.3, 2.4 Hz), 3.72 (dq, 1H, OC*H*H, $^2J$=9.7 Hz, $^3J$=7.1 Hz), 3.99 (dq, 1H,

OCH*H*, $^{2}J$=9.7 Hz, $^{3}J$=7.1 Hz), 5.13 (tq, 1H, H-4a, $^{3}J$=7.3 Hz, $^{5}J_{H,F}$=2.2 Hz), 5.32 (dd, 1H, H-3, $^{3}J$=7.6, 2.4 Hz), 6.95 (dd, 1H, H-6, $^{3}J$=8.8 Hz), 7.42 (dd, 1H, H-7, $^{3}J$=8.8 Hz, $^{4}J$=2.7 Hz), 7.92 (d, 1H, H-9, $^{4}J$=2.7 Hz); $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ 94.80 (d, $CF_3$, $^{5}J_{F,H}$=2.2 Hz). Anal. Calcd for $C_{15}H_{12}ClF_3O_4$: C, 51.67; H, 3.47. Found: C, 51.68; H, 3.32.

#### 4.4.4. 3-Ethoxy-1-(1,1,2,2-tetrafluoroethyl)-4,4a-dihydro-3H,10H-pyrano[4,3-b]chromen-10-one (**8j**)

Yield 72%, mp 130–132 °C; IR (KBr) 1675, 1618, 1579, 1476, 1465 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.29 (t, 3H, Me, $J$=7.1 Hz), 2.45 (dt, 1H, C*H*H, $^{2}J$=13.9 Hz, $^{3}J$=7.9 Hz), 2.59 (ddd, 1H, CH*H*, $^{2}J$=13.9 Hz, $^{3}J$=7.5, 2.3 Hz), 3.71 (dq, 1H, OC*H*H, $^{2}J$=9.7 Hz, $^{3}J$=7.1 Hz), 4.00 (dq, 1H, OCH*H*, $^{2}J$=9.7 Hz, $^{3}J$=7.1 Hz), 5.14 (td, 1H, H-4a, $^{3}J$=7.5 Hz, $^{5}J_{H,F}$=4.1 Hz), 5.23 (dd, 1H, H-3, $^{3}J$=8.1, 2.1 Hz), 6.81 (ddd, 1H, $CF_2CF_2H$, $^{2}J_{H,F}$=54.4, 53.2 Hz, $^{3}J_{H,F}$=11.2 Hz), 6.99 (dd, 1H, H-6, $^{3}J$=8.4 Hz, $^{4}J$=1.0 Hz), 7.07 (ddd, 1H, H-8, $^{3}J$=8.0, 7.2 Hz, $^{4}J$=1.0 Hz), 7.50 (ddd, 1H, H-7, $^{3}J$=8.4, 7.2 Hz, $^{4}J$=1.7 Hz), 7.93 (dd, 1H, H-9, $^{3}J$=8.0 Hz, $^{4}J$=1.7 Hz). Anal. Calcd for $C_{16}H_{14}F_4O_4$: C, 55.50; H, 4.08. Found: C, 55.46; H, 4.22.

#### 4.4.5. 3-Ethoxy-4,4a-dihydro-3H,10H-pyrano[4,3-b]-chromen-10-one (**8m**)

This compound was prepared according to the literature procedure.[3c] Yield 74%, mp 177–178 °C (lit.[3c] mp 177 °C, lit.[4] mp 176–177 °C); $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.30 (t, 3H, Me, $J$=7.1 Hz), 2.33 (dt, 1H, C*H*H, $^{2}J$=13.0 Hz, $^{3}J$=9.9 Hz), 2.59 (ddd, 1H, CH*H*, $^{2}J$=13.0 Hz, $^{3}J$=6.7, 2.1 Hz), 3.69 (dq, 1H, OC*H*H, $^{2}J$=9.5 Hz, $^{3}J$=7.1 Hz), 4.03 (dq, 1H, OCH*H*, $^{2}J$=9.5 Hz, $^{3}J$=7.1 Hz), 5.19 (ddd, 1H, H-4a, $^{3}J$=9.9, 6.7 Hz, $^{4}J$=1.4 Hz), 5.21 (dd, 1H, H-3, $^{3}J$=10.0, 2.1 Hz), 6.95 (dd, 1H, H-6, $^{3}J$=8.3 Hz, $^{4}J$=1.0 Hz), 7.05 (ddd, 1H, H-8, $^{3}J$=7.9, 7.3 Hz, $^{4}J$=1.0 Hz), 7.45 (ddd, 1H, H-7, $^{3}J$=8.3, 7.3 Hz, $^{4}J$=1.8 Hz), 7.56 (d, 1H, H-1, $^{4}J$=1.4 Hz), 7.95 (dd, 1H, H-9, $^{3}J$=7.9 Hz, $^{4}J$=1.8 Hz).

### 4.5. General procedure for pyridines (9c,e,h) and (10a,e)

A mixture of pyran **6** or **8** (1.0 mmol) and ammonium acetate (1.0 g, 13.0 mmol) in ethanol (4 mL) was refluxed for 7–8 h. The resulting reaction mixture was cooled and diluted with water (20 mL). The solid product obtained at standing was collected by filtration, dried and recrystallized from a toluene/hexane mixture to give compounds **9** and **10** as colourless crystals. In the case of **10e**, extraction with $CHCl_3$ was needed.

#### 4.5.1. 3-(2′-Hydroxy-5′-methylbenzoyl)-5-(3-hydroxypropyl)-2-(trifluoromethyl)pyridine (**9c**)

Yield 71%, mp 101–102 °C; IR (KBr) 3412, 1635, 1618, 1588, 1570, 1482 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.48 (br s, 1H, OH), 1.91–1.98 (m, 2H, $CH_2$), 2.91 (t, 2H, Py–$CH_2$, $^{3}J$=7.8 Hz), 3.73 (br t, 2H, $OCH_2$, $^{3}J$=6.0 Hz), 6.82 (br d, 1H, H-6′, $^{4}J$=2.0 Hz), 6.99 (d, 1H, H-3′, $^{3}J$=8.5 Hz), 7.37 (dd, 1H, H-4′, $^{3}J$=8.5 Hz, $^{4}J$=2.0 Hz), 7.61 (d, 1H, H-4, $^{4}J$=1.8 Hz), 8.73 (d, 1H, H-6, $^{4}J$=1.8 Hz), 11.54 (s, 1H, OH); $^{19}$F NMR (376.5 MHz, $CDCl_3$) $\delta$ 98.58 (s, $CF_3$). Anal. Calcd for $C_{17}H_{16}F_3NO_3$: C, 60.18; H, 4.75; N, 4.13. Found: C, 60.20; H, 4.81; N, 4.15.

#### 4.5.2. 3-(5′-Chloro-2′-hydroxybenzoyl)-5-(3-hydroxypropyl)-2-(trifluoromethyl)pyridine (**9e**)

Yield 67%, mp 103–104 °C; IR (KBr) 3403, 1636, 1617, 1575, 1472 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.43 (br s, 1H, OH), 1.92–1.99 (m, 2H, $CH_2$), 2.92 (t, 2H, Py–$CH_2$, $^{3}J$=7.7 Hz), 3.74 (t, 2H, $OCH_2$, $^{3}J$=6.0 Hz), 7.03 (d, 1H, H-6′, $^{4}J$=2.6 Hz), 7.06 (d, 1H, H-3′, $^{3}J$=9.0 Hz), 7.50 (dd, 1H, H-4′, $^{3}J$=9.0 Hz, $^{4}J$=2.6 Hz), 7.61 (d, 1H, H-4, $^{4}J$=1.5 Hz), 8.76 (d, 1H, H-6, $^{4}J$=1.5 Hz), 11.61 (s, 1H, OH); $^{19}$F NMR (376 MHz, $CDCl_3$, HFB) $\delta$ 98.67 (s, $CF_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 29.03, 33.04, 61.29, 119.89, 120.45, 121.23 (q, $CF_3$, $^{1}J_{C,F}$=275.2 Hz), 124.06, 131.60, 131.67, 135.87, 137.68, 140.72, 142.30 (q, *C*–$CF_3$, $^{2}J_{C,F}$=35.0 Hz), 151.19, 161.73, 198.11. Anal. Calcd for $C_{16}H_{13}ClF_3NO_3$: C, 53.42; H, 3.64; N, 3.89. Found: C, 53.54; H, 3.58; N, 3.81.

#### 4.5.3. 3-(2′-Hydroxy-5′-nitrobenzoyl)-5-(3-hydroxypropyl)-2-(trifluoromethyl)pyridine (**9h**)

Yield 40%, mp 128–129 °C; IR (KBr) 3421, 1640, 1625, 1575, 1531, 1473, 1347, 1329 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.43 (br s, 1H, OH), 1.93–2.01 (m, 2H, $CH_2$), 2.95 (t, 2H, Py–$CH_2$, $^{3}J$=7.6 Hz), 3.73 (t, 2H, $OCH_2$, $^{3}J$=6.0 Hz), 7.23 (d, 1H, H-3′, $^{3}J$=9.2 Hz), 7.67 (d, 1H, H-4, $^{4}J$=1.6 Hz), 8.08 (d, 1H, H-6′, $^{4}J$=2.7 Hz), 8.43 (dd, 1H, H-4′, $^{3}J$=9.2 Hz, $^{4}J$=2.7 Hz), 8.81 (d, 1H, H-6, $^{4}J$=1.6 Hz), 12.30 (s, 1H, OH). Anal. Calcd for $C_{16}H_{13}F_3N_2O_5$: C, 51.90; H, 3.54; N, 7.57. Found: C, 51.84; H, 3.33; N, 7.34.

#### 4.5.4. 3-Salicyloyl-2-(difluoromethyl)pyridine (**10a**)

Yield 55%, mp 96–97 °C; IR (KBr) 1632, 1617, 1576, 1485 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.78 (t, 1H, $CF_2H$, $^{2}J_{H,F}$=54.6 Hz), 6.85 (ddd, 1H, H-5′, $^{3}J$=8.0, 7.3 Hz, $^{4}J$=1.1 Hz), 7.09 (dd, 1H, H-3′, $^{3}J$=8.5 Hz, $^{4}J$=1.0 Hz), 7.18 (dd, 1H, H-6′, $^{3}J$=8.0 Hz, $^{4}J$=1.6 Hz), 7.53–7.58 (m, 2H, H-4′, H-5), 7.79 (br d, 1H, H-4, $^{3}J$=8.2 Hz), 8.85 (dd, 1H, H-6, $^{3}J$=4.8 Hz, $^{4}J$=1.4 Hz), 11.76 (s, 1H, OH); $^{1}$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.95 (ddd, 1H, H-5′, $J$=8.0, 7.2, 1.0 Hz), 6.99 (dd, 1H, H-3′, $J$=8.3, 0.8 Hz), 7.02 (t, 1H, $CF_2H$, $^{2}J_{H,F}$=53.9 Hz), 7.41 (dd, 1H, H-6′, $J$=7.9, 1.6 Hz), 7.56 (ddd, 1H, H-4′, $J$=8.4, 7.2, 1.8 Hz), 7.69 (br dd, 1H, H-5, $^{3}J$=7.9, 4.8 Hz), 7.98 (br d, 1H, H-4, $^{3}J$=7.9 Hz), 8.84 (dd, 1H, H-6, $^{3}J$=4.8 Hz, $^{4}J$=1.5 Hz), 10.89 (s, 1H, OH); $^{19}$F NMR (376 MHz, DMSO-$d_6$, HFB) $\delta$ 48.60 (d, $CF_2H$, $^{2}J_{F,H}$=53.9 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 112.6 (t, $CF_2H$, $^{1}J_{C,F}$=239.6 Hz), 117.6, 119.4, 121.9, 125.3, 132.1, 134.3 (t, C-3, $^{3}J_{C,F}$=2.4 Hz), 136.3, 136.8, 148.2 (t, C-2, $^{2}J_{C,F}$=23.6 Hz), 150.5, 159.8, 196.7 (C=O). Anal. Calcd for $C_{13}H_9F_2NO_2$: C, 62.65; H, 3.64; N, 5.62. Found: C, 62.77; H, 3.74; N, 5.49.

#### 4.5.5. 3-(5′-Chloro-2′-hydroxybenzoyl)-2-(trifluoromethyl)-pyridine (**10e**)

Yield 42%, mp 104–105 °C; IR (KBr) 1628, 1611, 1585, 1468 cm$^{-1}$; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.03 (d, 1H, H-6′, $^{4}J$=2.6 Hz), 7.07 (d, 1H, H-3′, $^{3}J$=9.0 Hz), 7.50 (dd, 1H, H-4′, $^{3}J$=9.0 Hz, $^{4}J$=2.6 Hz), 7.68 (dd, 1H, H-5, $^{3}J$=7.8, 4.8 Hz), 7.80 (dd, 1H, H-4, $^{3}J$=7.8 Hz, $^{4}J$=1.0 Hz), 8.93 (dd, 1H, H-6, $^{3}J$=4.8 Hz, $^{4}J$=1.0 Hz), 11.60 (s, 1H, OH); $^{19}$F NMR (376 MHz, $CDCl_3$, HFB) $\delta$ 98.36 (d, $CF_3$, $^{5}J_{F,H}$=0.6 Hz). Anal. Calcd for $C_{13}H_7ClF_3NO_2$: C, 51.76; H, 2.34; N, 4.64. Found: C, 51.67; H, 2.27; N, 4.56.

### 4.6. Crystal data for 6a

$C_{16}H_{14}F_2O_4$, triclinic crystals space group $P\bar{1}$, at 295(2) K, $a$=8.20 50(5), $b$=9.4468(6), $c$=10.4422(6) Å, $\alpha$=90.326(7)°, $\beta$=108.959(5)°, $\gamma$=114.490(5)°, $V$=687.28(7) Å$^3$, $d_{calcd}$=1.490 g cm$^{-3}$, absorption coefficient $\mu$=0.124 mm$^{-1}$, $Z$=2. The intensities of 4064 ($R_{int}$=0.0140) were measured on a 'Xcalibur 3' automatic four-circle diffractometer (Mo K$\alpha$ radiation, $\lambda$=0.71093 Å, graphite monochromator, $\omega/2\theta$ scan, $2\theta_{max}$=52°). The structure was solved by direct methods with the use of the SHELXTL program package.[15] Nonhydrogen atoms were refined by full-matrix least-squares procedures (with $F^2$) in an anisotropic approximation. The positions of hydrogen atoms were found by a difference Fourier synthesis and refined in an isotropic approximation. The final discrepancy factors $R_1$=0.0397, $wR_2$=0.1016, Goof=1.005 for 2284 reflections with $I>2\sigma(I)$, $R_1$=0.0766, $wR_2$=0.1098 (all data). Largest different peak and hole: 0.207 and −0.167 e Å$^{-3}$. Completeness to $\theta$=26.00° (96.0%). Deposition number CCDC 646177.

### 4.7. Crystal data for 8e

$C_{15}H_{12}ClF_3O_4$, monoclinic crystals space group $C2/c$, at 295(2) K, $a$=26.0377(9), $b$=8.1555(3), $c$=15.7100(5) Å, $\beta$=116.099(5)°, $V$=2995.87(18) Å$^3$, $d_{calcd}$=1.546 g cm$^{-3}$, absorption coefficient

$\mu$=0.305 mm$^{-1}$, $Z$=8. The intensities of 4716 ($R_{int}$=0.0234) were measured on a 'Xcalibur 3' automatic four-circle diffractometer (Mo K$\alpha$ radiation, $\lambda$=0.71093 Å, graphite monochromator, $\omega/2\theta$ scan, $2\theta_{max}$=65°). The structure was solved by direct methods with the use of the SHELXTL program package.[15] Nonhydrogen atoms were refined by full-matrix least-squares procedures (with $F^2$) in an anisotropic approximation. The positions of hydrogen atoms were found by a difference Fourier synthesis and refined in an isotropic approximation. The final discrepancy factors $R_1$=0.0394, $wR_2$=0.1044, Goof=1.001 for 2359 reflections with $I>2\sigma(I)$, $R_1$=0.0750, $wR_2$=0.1094 (all data). Largest different peak and hole: 0.141 and −0.346 e Å$^{-3}$. Completeness to $\theta$=26.50° (98.3%). Deposition number CCDC 689992.

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