Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 10549–10561

Limitations of the Wittig–Horner-type annulation of fluorobutenolide moiety to 3-hydroxyquinoline-2,4(2*H*,3*H*)-diones. Novel modifications of the Perkow reaction including fluorinated acyloxy leaving groups

Karel Pomeisl,[a,*] Jaroslav Kvíčala,[b] Oldřich Paleta,[b] Antonín Klásek,[c] Stanislav Kafka,[c] Vladislav Kubelka,[d] Jaroslav Havlíček[d] and Jan Čejka[e]

[a]*Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague, Czech Republic*
[b]*Department of Organic Chemistry, Prague Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic*
[c]*Enviromental Department of Chemistry and Environmental Technology, Tomáš Bat'a University, Nám. TGM 275, 762 72 Zlín, Czech Republic*
[d]*Zentiva, U Kabelovny 130, 102 37 Prague 10, Czech Republic*
[e]*Department of Solid State Chemistry, Prague Institute of Chemical Technology, Technická 5, 166 28 Prague 6, Czech Republic*

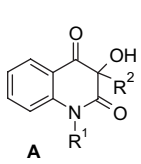
Received 26 January 2007; revised 29 June 2007; accepted 19 July 2007
Available online 26 July 2007

Dedicated to Professor Miloslav Ferles on the occasion of his 85th birthday

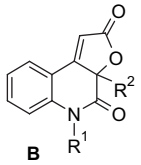
Abstract—3-(Fluoroacyloxy)quinoline-2,4(1*H*,3*H*)-diones react with triethyl phosphite to afford either the product of the Perkow reaction or the corresponding 4-ethoxyquinolin-2(1*H*)-one. In both reactions, the fluorocarboxylate anion acts as the leaving group. For the corresponding 3-(fluoroiodoacetoxy) derivative this observation precludes the application of the intramolecular Wittig–Horner synthesis to modify quinoline-2,4(1*H*,3*H*)-diones by the annulation of a fluorinated but-2-enolide moiety.

1. Introduction

Substituted quinoline-2,4(1*H*,3*H*)-diones (**A**) as metabolites of some *Pseudomonas* species exhibited interesting bioactivity[1] initiating the search for novel classes of non-steroidal anti-inflammatory agents based on the lead structure **A**.[2] As a γ-lactone moiety attached to an aromatic cycle system showed strong anti-inflammatory activity,[3] some substituted 3-hydroxyquinoline-2,4(1*H*,3*H*)-diones were modified by the annulation of the but-2-enolide cycle (type **B**).[4] The annulation was carried out by the Wittig strategy at C-4-carbonyl group using (ethoxycarbonylmethylene)-triphenylphosphorane or more conveniently at C-3-hydroxyl group via 3-(bromoacetoxy)derivative and the subsequent 3-(2-triphenylphosphonioacetoxy)derivative.[4]



A



B

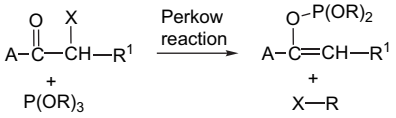
A further modification of the properties of the compounds **B** can be carried out by the introduction of halogen atoms and groups in the butenolide moiety. Fluoro substituents, such as F, CF_3 or OCF_3 are powerful modifiers of chemical and biological properties of organic compounds.[5] A combination of fluorine substituents with but-2-en-4-olide cycle could thus afford compounds with new and interesting bioactivity.[6] Wittig–Horner-type reactions have been applied to the syntheses of monofluorinated butenolide compounds using fluorohalogenoacetates as the building blocks affording the desired products in good yields.[7] The reactions proceeded with complete stereoselectivity resulting in configurations suitable for the subsequent cyclization.[7a,b]

However, when 1-benzyl-3-butyl-3-(fluoroiodoacetoxy)quinoline-2,4(1*H*,3*H*)-dione (**9a**) was reacted with triethyl

Keywords: Wittig–Horner synthesis; Lithium 2-(diethoxyphosphoryl)-2-fluoroacetate; 3-Halogenoacyloxyquinoline-2,4(1*H*,3*H*)-diones; Fluorofuranone; But-2-enolide, Perkow reaction; ^{19}F NMR reaction profile; Cytostatic activity; Chronic myeloid leukemia; Breast carcinoma.
* Corresponding author. Tel.: +420 220 183 475; fax: +420 220 183 560; e-mail: pomeisl@uochb.cas.cz

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.058

phosphite the unexpected product **17a** (Scheme 3) was obtained instead of the assumed Wittig–Horner intermediate **10a** (Scheme 2). The formation of the product **17a** corresponds to a novel modification of the Perkow reaction.[8] As is known from the literature, the Wittig–Horner synthesis[9] cannot be applied when a carbonyl group is present in the α-position relative to the carbon–halogen bond, because enol phosphites are formed instead of phosphonates according to the general equation of the Perkow reaction (1).[10a]



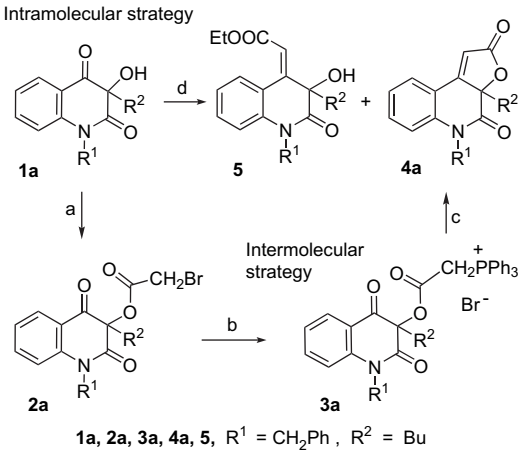
(1)

Halogenated ketones, diketones, aldehydes, esters, amides, acyl halides,[10a,b] polycyclic compounds,[10c,d] α-halogenonitroalkanes,[10a] and 1,3-dichloro-1,1,3,3-tetrafluoroacetone[10e] react in this manner. The leaving groups in halogeno compounds are halogen anions. In one case, the Perkow reaction with an acetoxy leaving group has been reported in the chemistry of D-fructose.[11]

In this paper, we report our findings on the limitations of a Wittig–Horner-type fluorobutenolide annulation to 3-hydroxyquinoline-2,4(2*H*,3*H*)-diones and approach our observations of novel modifications of the Perkow reaction, in which halogenated acyloxy anions are the new leaving groups.

2. Results and discussion

Firstly, we attempted the annulation of the but-2-en-4-olide cycle to 1-benzyl-3-butyl-3-hydroxy-quinoline-2,4(2*H*,3*H*)-dione (**1a**). The recently reported procedures[4] used the intramolecular Wittig-type synthesis (Scheme 1): The reaction of **1a** with bromoacetyl bromide afforded bromoacetyl derivative **2a**, which was transformed to phosphonium salt **3a** by reaction with triphenylphosphane. Compound **3a** was difficult to purify for analyses, because it was spontaneously converted to **4a** at room temperature. However, the subsequent treatment of **3a** with 0.5 M NaOH results in the complete closure to obtain the target furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-dione **4a**.

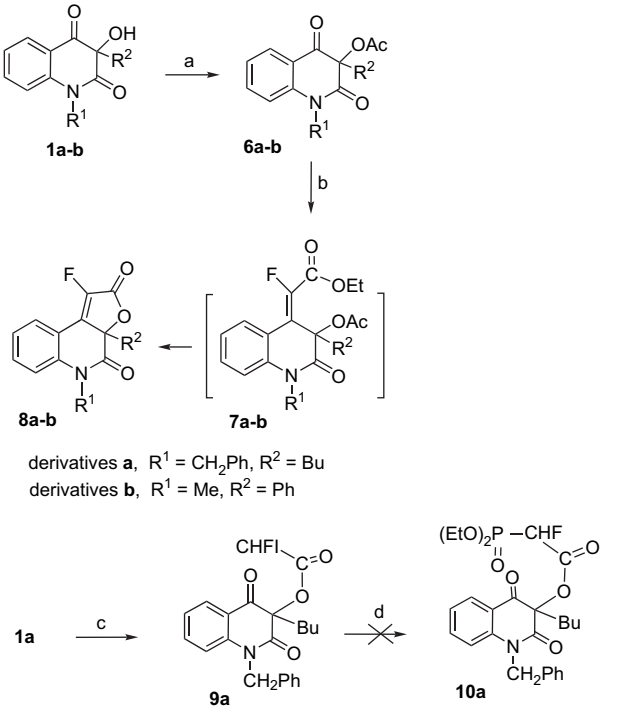


Scheme 1. Reagents and conditions: (a) $BrCH_2C(O)Br$, 65%; (b) PPh_3, C_6H_6, Δ, 61%; (c) aq 0.5 M NaOH, $CHCl_3$, 52%; (d) $Ph_3P{=}CHC(O)OEt$, Δ, 68%.

On the other hand, the intermolecular synthesis involving ethyl (triphenylphosphoranylidene)acetate[4a] afforded the non-cyclizable (*E*)-4-(ethoxycarbonyl)methylene derivative **5** (yield 68%) and only negligible amount (ca. 0.5%) of the desired **4a** (Scheme 1).

In contrast, the analogous reaction of **1a** with the Wittig–Horner reagent, alkyl (diethoxyphosphoryl)fluoroacetate, proceeded with only low conversion of starting material to form desired products with cyclizable configuration (vide infra).[7b,12]

In the synthesis of the desired 5-fluorofuro[2,3-*c*]quinoline-2,4-(3a*H*,5*H*)-diones **8a**,**b** (Scheme 2), the Wittig–Horner intramolecular strategy involving 2-fluoro-2-iodoacetate **9a** was also unsuccessful, because the (diethoxyphosphoryl)-fluoroacetate **10a** was not formed. Instead, an unexpected product corresponding to a novel modification of the Perkow reaction was obtained (vide infra). In the intermolecular strategy, the reaction of the acetates **6a**,**b** with lithium salt of ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate[7b,12] afforded directly the final products **8a**,**b** (Scheme 2), as the Wittig–Horner products (*E*)-**7a**,**b** cyclized rapidly, but the yields of **8a**,**b** were surprisingly very low (ca. 2 and 16%, respectively).



Scheme 2. Reagents and conditions: (a) AcCl, Py, CH_2Cl_2, −20 °C to rt, 73–82%; (b) $(EtO)_2P(O)CHFC(O)OEt$, *n*-BuLi, THF, −78 °C; (c) IFHC-C(O)Cl, Py, CH_2Cl_2, 48%; (d) $P(OEt_3)$, toluene, Δ.

To obtain further information about the reaction course, the reaction mixture leading potentially to **8a**,**b** was monitored by ^{19}F NMR within the interval of −70 to 25–35 °C (Figs. 1–3). As shown in Figure 1, fluorophosphonate **11** was completely converted to its lithium salt **12** (^{19}F NMR signal −229.1 ppm) by *n*-butyllithium at −70 °C, while at higher temperatures the portion of the unreacted **11** increased with increasing temperature.

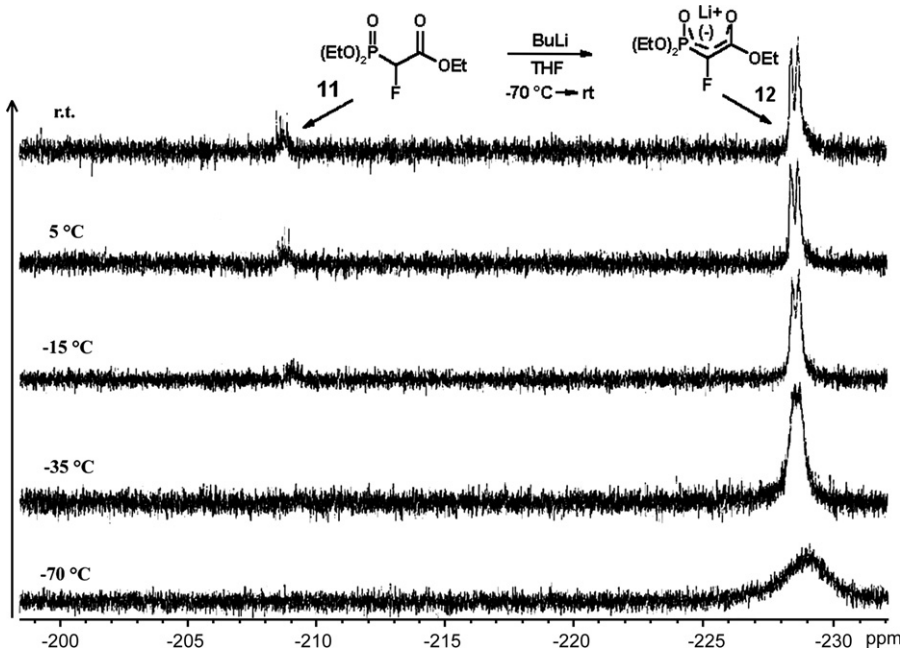


Figure 1. ^{19}F NMR temperature profile (−70 °C to >rt) of the equilibrium of fluorophosphonate **11** and its lithium salt **12** (~89% content in the mixture).

A temperature profile of the reaction mixture of lithium phosphonate **12** and **6a** (Scheme 2) is depicted in Figure 2. The ^{19}F NMR signal of **8a** (−144.1 ppm) did not occur at temperatures below −10 °C and only patterns of **8a** could be observed in the reaction mixture. At higher temperatures, phosphonate salt **12** was decomposed (−201.2 ppm, **13**) and therefore the product **8a** was formed only in a small yield.

A similar temperature profile was observed for the reaction of lithium phosphonate **12** and quinolinedione **6b** (Scheme 2, Fig. 3). The last scan corresponds the state of the reaction mixture after 2 h 45 min reaction: phosphonate was completely decomposed and the product **8b** was present in a low concentration. These results are in contrast with the relatively easy reactions employing the Wittig reagents in the preparation of **4a** (Scheme 1).

We have mentioned above (Scheme 2) that 2-fluoro-2-iodoacetyl derivative **9a**, which was formed by the treatment of **1a** with fluoroiodoacetyl chloride, afforded an unexpected product in the reaction with triethyl phosphite. This compound is enol phosphate **17a** as depicted in Scheme 3. Its

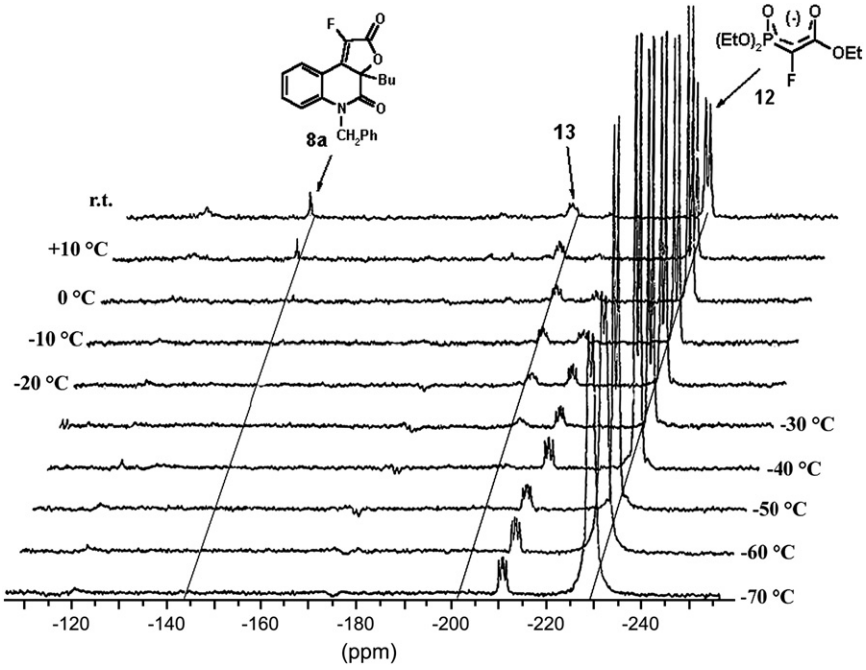


Figure 2. ^{19}F NMR temperature profile (−70 °C to >rt) of the reaction of lithium fluorophosphonate **12** with 3-acetoxyquionoline-2,4-dione **6a** to afford the target **8a** (~2% content in the mixture).

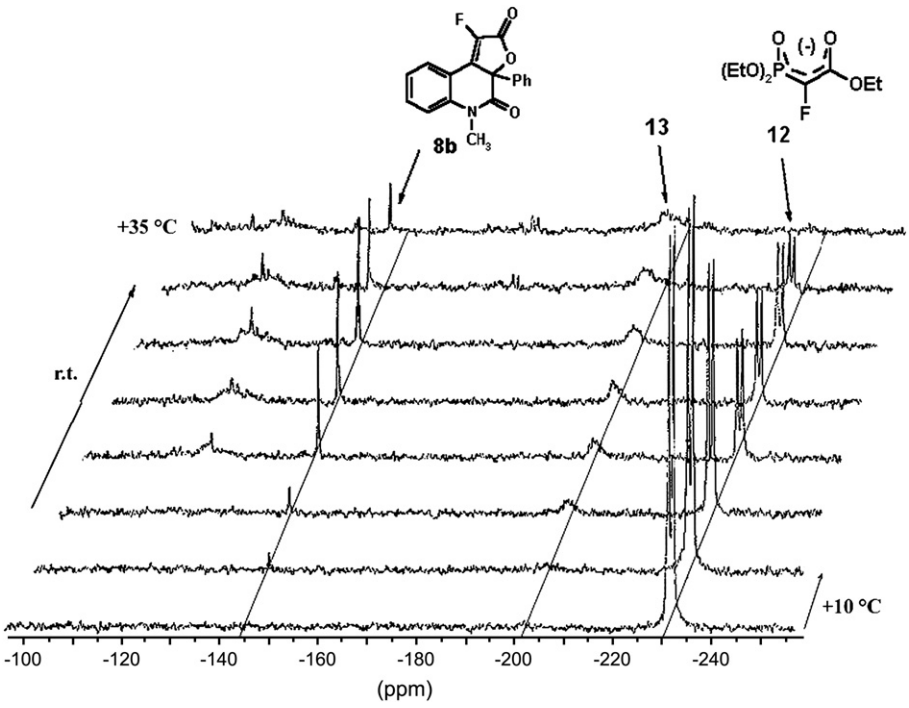
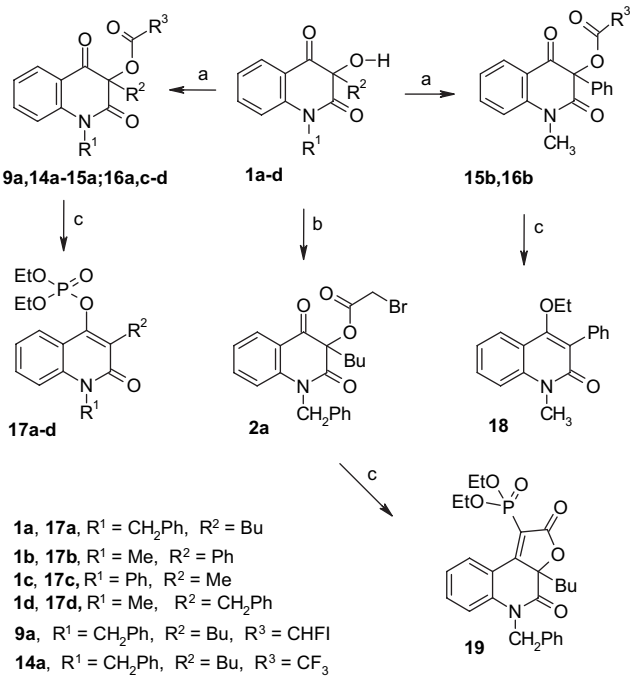


Figure 3. ^{19}F NMR temperature profile (+10 to >+35 °C) of the reaction of fluorophosphonate **12** with 3-acetoxyquionoline-2,4-dione **6b** to afford the target **8b** (~16% content in the mixture).

formation has corresponded a new modification of the Perkow reaction involving 2-fluoro-2-iodoacetate anion ($CHFICOO^-$) as the leaving group. Departure of acetate ion in the Perkow reaction has been observed only once before in the reaction of pentaacetylated D-fructose with trimethyl phosphite.[11] This rather unusual transformation may be attributed to the structural nature of the sugar skeleton and its multiple acetoxy groups. Surprisingly, we have found that the 3-acetoxyquinoline-2,4(1*H*,3*H*)-diones **6a**,**b** bearing acetoxy group did not react (Table 1, entries 2 and 3). Thus, we assumed that acyloxy groups having a higher electronegativity than the acetyloxy group could act as leaving groups in the new modification of the Perkow reaction.

We prepared a series of 3-(halogenoacyloxy)quinoline-2,4(1*H*,3*H*)-diones, viz. **14a–c**, **15a**,**b**, and **16a–d** to study their ability to act as the leaving groups. The results of the study are summarized in Scheme 3 and Table 1 (entries 5–13). According to Scheme 3, the reactions of **2a**, **14a–c**, **15a**,**b**, and **16a–d** afforded three kinds of products: the products of the Perkow reaction (**17a–d**), 1-methyl-4-ethoxyquinolin-2(1*H*)-one (**18**) and the compound **19** possessing an annulated furanone moiety. In the first two reactions, the halocarboxylate anion was eliminated. The role of halocarboxylates as leaving groups in the Perkow reaction is previously undescribed feature. In both the reactions shown in the Scheme 3, the elimination of the acyloxy moiety results in energetically favored extension in conjugation of the π-system of the heterocyclic cycle. In the reactions of the halogenoacyl derivatives, the carbonyl groups in the acyl R^3–CO or at C-4 of the heterocyclic cycle are attacked by the phosphorus atom of triethyl phosphite (Scheme 4). Also in the reaction of the fluoroiodoacetyl derivative **9a**, triethyl phosphite attacks C-4 of the heterocyclic cycle to form



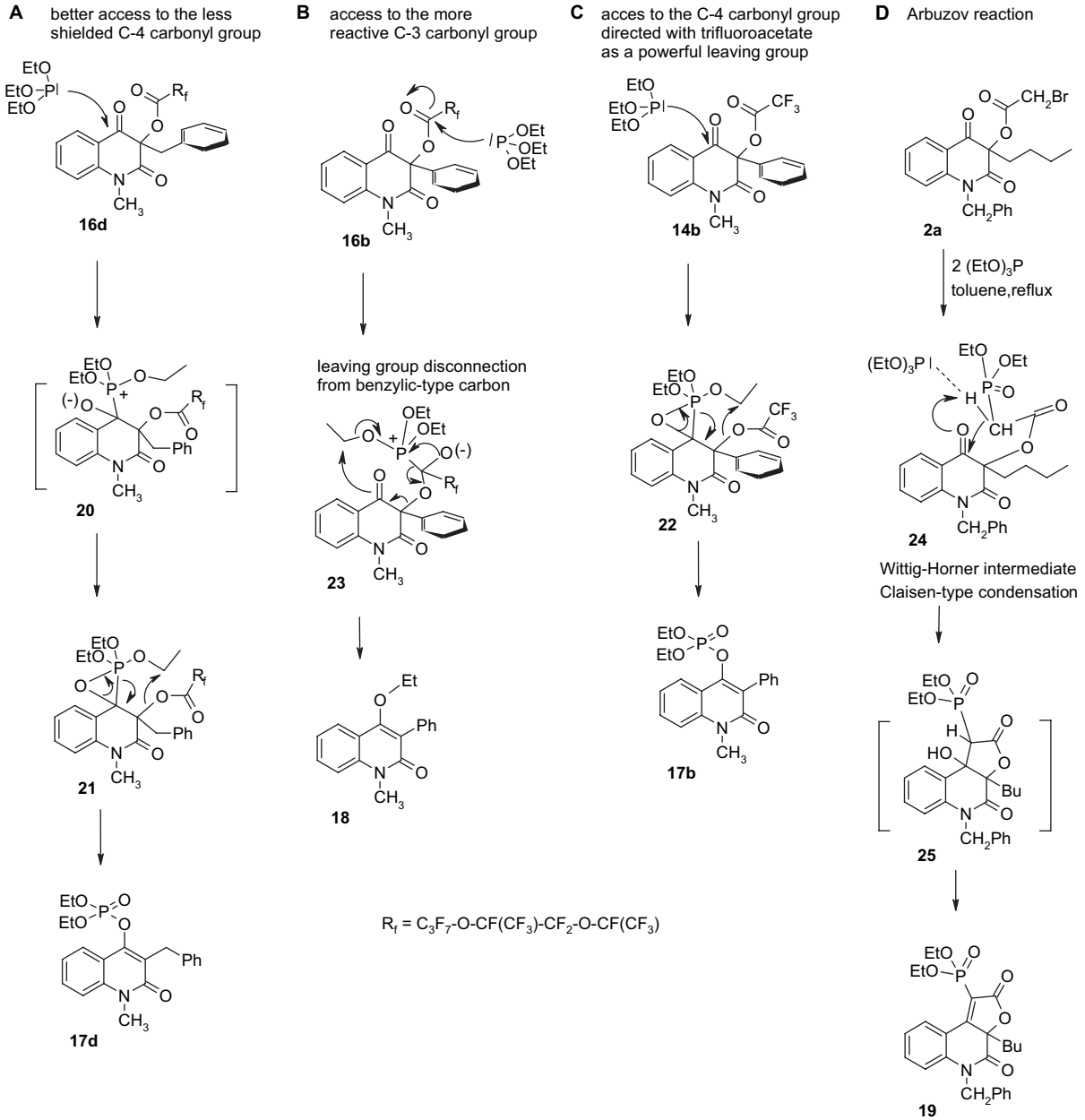
1a, **17a**, R^1 = CH_2Ph, R^2 = Bu
1b, **17b**, R^1 = Me, R^2 = Ph
1c, **17c**, R^1 = Ph, R^2 = Me
1d, **17d**, R^1 = Me, R^2 = CH_2Ph
9a, R^1 = CH_2Ph, R^2 = Bu, R^3 = CHFI
14a, R^1 = CH_2Ph, R^2 = Bu, R^3 = CF_3
14b, R^1 = Me, R^2 = Ph, R^3 = CF_3
14c, R^1 = Ph, R^2 = Me, R^3 = CF_3
15a, R^1 = CH_2Ph, R^2 = Bu, R^3 = $CClF_2$-CClF
15b, R^1 = Me, R^2 = Ph, R^3 = $CClF_2$-CClF
16a, R^1 = CH_2Ph, R_2 = Bu, R_3 = C_3F_7O-$CF(CF_3)CF_2O$-$CF(CF_3)$
16b, R^1 = Me, R_2 = Ph, R_3 = C_3F_7O-$CF(CF_3)CF_2O$-$CF(CF_3)$
16c, R^1 = Ph, R_2 = Me, R_3 = C_3F_7O-$CF(CF_3)CF_2O$-$CF(CF_3)$
16d, R^1 = Me, R_2 = CH_2Ph, R_3 = C_3F_7O-$CF(CF_3)CF_2O$-$CF(CF_3)$

Scheme 3. Reagents and conditions: (a) R^3–C(O)X, Py, CH_2Cl_2; (b) $BrCH_2C(O)Cl$, Py, C_6H_6, 65%; (c) P(OEt), toluene, Δ, 11–68% (see Table 1).

Table 1. Reaction of halogenoacyl-substituted quinoline-2,4(1*H*,3*H*)-diones with triethyl phosphite

Entry	Starting compound				Product	
	No.	R^1	R^2	Leaving group R^3-$COO^{(-)}$	No.	Yield[a] (%)
1	**2a**	Bn	Bu	CH_2Br	**19**[b]	52
2	**6a**	Bn	Bu	CH_3	—	—
3	**6b**	Me	Ph	CH_3	—	—
4	**9a**	Bn	Bu	CHFI	**17a**	68
5	**14a**	Bn	Bu	CF_3	**17a**	36
6	**14b**	Me	Ph	CF_3	**17b**	36
7	**14c**	Ph	Me	CF_3	**17c**	31
8	**15a**	Bn	Bu	$CClF_2$–CClF	—	—
9	**15b**	Me	Ph	$CClF_2$–CClF	**18**	27
10	**16a**	Bn	Bu	C_3F_7O–$CF(CF_3)$–CF_2O–$CF(CF_3)$	**17a**	18
11	**16b**	Me	Ph	C_3F_7O–$CF(CF_3)$–CF_2O–$CF(CF_3)$	**18**	11
12	**16c**	Ph	Me	C_3F_7O–$CF(CF_3)$–CF_2O–$CF(CF_3)$	**17c**	21
13	**16d**	Me	Bn	C_3F_7O–$CF(CF_3)$–CF_2O–$CF(CF_3)$	**17d**	54

[a] Isolated unoptimized yields.
[b] The structure of **19** was determined by NMR and X-ray analysis (see Supplementary data).



Scheme 4. The proposed mechanisms of the modified Perkow reaction and Claisen-type condensation.

Perkow product instead of corresponding product of Arbuzov reaction as is usual for the alkyl fluoroiodoacetates.[7b]

As the acetoxy derivatives **6a** or **6b** did not react at all (Table 1, entries 2 and 3) it can be inferred that the new reactions (Scheme 1) require the presence of a stronger electron-withdrawing acyl group. Halogenated acyloxy groups possess a more reactive carbonyl group and as such are better leaving groups. Perhaps the increase in reactivity of the C-4-carbonyl group is also due to halogenated acyloxy group. In any case, the two carbonyl groups are preferential reaction sites for the attack by the phosphorus atom of triethyl phosphite in compounds **9a** and **14**–**16** (Scheme 4).

The directing factors of the phosphite attack to form the enol phosphates **17a**–**d**, the usual products of the Perkow reaction, or the unusual Perkow product **18** may be formulated as follows: as the Perkow reaction leading to the Perkow products **17a**–**d** was observed for all the compounds that possess an aliphatic (butyl, methyl) or benzyl substituent at C-3 (**9a**, **14a**–**c**, and **16a**,**c**,**d**). The nucleophilic attack then occurs at the cycle C-4 carbonyl group. (Scheme 4; see pathway A). The proposed mechanism for compound **16d** via intermediates **20** and **21** featuring the fluorinated acyloxy leaving group corresponds to proposed mechanisms[10a,d,13] of the Perkow reaction. In contrast, the product **18** is most likely the result of an attack of the acyl-carbonyl moiety in the derivatives **15b** and **16b** (Scheme 4; see pathway B). Both compounds possess a rigid phenyl substituent at C-3. In the case of **15b** or **16b**, the triethyl phosphite nucleophile attacks the more reactive carbonyl carbon in the ester group, which is probably less shielded or its reactivity increased by a different electronic effect of phenyl substituent in contrast to, e.g., butyl or benzyl.[14] However, if this idea is correct, **14b** should be rather transformed to **18** than **17b** via intermediate **22** (Scheme 4, see pathway C). We have no explanation for the unexpected outcome but note that trifluoroacetate is a particularly good substituted acetate leaving group. This may exert a powerful effect on the outcome of the Perkow reaction.

An analogous mechanism to the formation of product **18** via **23** featuring fluoride anion as a leaving group was proposed (reported) previously for the reaction of perfluorinated aliphatic ketones with trialkyl phosphites.[10e] The products **17a**–**d** and **18** were obtained in isolated yields of 18–68% and 11–27% (Table 1), owing in part to the difficulties with their separation. In fact, the reactions reached almost complete conversions of the starting acyloxy compounds **9**–**16** after 2–26 h, and the isolated products **17a**–**d** or **18** were the major or exclusive compounds in the reaction mixtures according to TLC analyses. From this point of view, the presented reactions included only unoptimized yields.

An unexpected product **19** possessing an annulated furanone moiety (Scheme 3) was obtained in the reaction of bromoacetyl derivative **2a** with triethyl phosphite in boiling toluene. Its formation could be explained by a lower reactivity of the carbonyl groups in the acyl R^3–CO and at C-4 of the heterocyclic cycle, which are not attacked by the phosphorus atom of triethyl phosphite. The hypothetical intermediates **24**,**25** and the proposed mechanism for formation of product **19** are depicted in Scheme 4 (see pathway D). The transformation of the intermediate **24** to **25** can be understood as a Claisen-type condensation.[15]

The obtained enol phosphates **17a**–**d** as products of the Perkow reaction displayed a significant cytostatic activity in cells K-562 (chronic myeloid leukemia) and MCF7 (breast carcinoma) compared with olomoucine as the most frequently examined cyclin-dependent kinase (CDK) inhibitor together with roscovitine[16] (Table 2, entries 1–4). The results also indicate that compounds **17a**–**c** exhibit a comparable or even a better cytostatic activity (inhibition of the cell growth in vitro) toward leukemic K-562 cells compared with roscovitine, while the bioactivity of these compounds toward breast carcinoma MCF7 is less sensitive. The most promising antiproliferative potency is exerted by compound **17a**. On the other hand, the bioactivity of phosphonate **19** decreased by annulation of the rigid but-2-enolide moiety (Table 2, entry 5).

Table 2. Bioactivity of enol phosphates **17** and **19**

Entry	Product			IC_{50}/μmol L^{-1}	
	No.	R^1	R^2	K-562[a]	MCF7[b]
1	**17a**	Bn	Bu	9.6	18.1
2	**17b**	Me	Ph	68.5	134.5
3	**17c**	Ph	Me	32.4	45.4
4	**17d**	Me	Bn	100.3	92.3
5	**19**	Bn	Bu	>167	>167
Olomoucine				150	134
Roscovitine				45	12

[a] Chronic myeloid leukemia.
[b] Breast carcinoma.

3. Conclusions

The reactions reported in this paper show that the application of the Horner–Wadworth–Emmons strategy for the annulation of the α-fluorobut-2-enolide cycle to hetero-(poly)cyclic systems may completely fail from two reasons: first, due to the low reactivity of lithium (diethoxyphosphoryl)-fluoroacetate reagent toward 3-acetyloxyquinoline-2,4(1*H*,3*H*)-dione substrates as verified by ^{19}F NMR study; second, trialkyl phosphite attacks preferentially highly reactive carbonyl groups in 3-(fluoroiodoacetoxy)quinoline-2,4(1*H*,3*H*)-diones to afford the product of the Perkow reaction. We have found that analogously reacted a number of 3-(fluoroacyloxy)quinoline-2,4(1*H*,3*H*)-diones. Thus, we developed the method for preparation of a new class of bioactive quinoline-2-one enol phosphates from easily available quinoline-2,4(1*H*,3*H*)-dione building blocks.

4. Experimental

4.1. General comments

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a Bruker WP 80 SY (FT, ^{19}F at 75.4 MHz), Bruker 400 AM (FT, ^{19}F at 376.5 MHz, ^{31}P at 202.5 MHz) and Gemini 300 (^1H at 300.1 MHz, ^{13}C at 75.5 MHz using ^1H decoupling) in $CDCl_3$ and tetrahydrofuran-d_8, respectively. Chemical shifts are reported relative to tetramethylsilane,

fluorotrichloromethane, and phosphorous acid as internal standards. IR spectra were recorded on a FTIR Spec. Nicolet 740 in $CHCl_3$. Mass spectra were scanned on a Autospec Ultima (Micromass) using GC (HP 6890, ionization with electron impact at 70 eV) and ZAB-EQ (VG Analytical) spectrometers using FAB (ionization with xenon, accelerating voltage 8 kV, glycerol matrix). Preparative TLC was carried out on 45×18×0.4 cm loose layer on silica gel containing UV indicator (system S1).

Chemicals used were as follows: quinoline-2,4-diones **1a–d** were obtained from Tomáš Bat'a University (Zlín, Czech Republic). Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate was prepared by several reactions from trifluorochloroethylene.[7b,17–19] 2,5-Bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoyl fluoride was synthesized as described in Ref. 20 and distilled at 115–117 °C. 2,3,3-Trifluoro-2,3-dichloropropanoyl chloride was prepared as described in Ref. 21 and distilled at 86–88 °C. Standard chemicals were purchased from Sigma–Aldich (Czech Republic). Pyridine, tetrahydrofuran, and methylene chloride were dried and purified according to standard procedures. 2-Fluoro-2-iodoacetyl chloride was prepared by the hydrolysis of ethyl 2-fluoro-2-iodoacetate followed by the treatment of corresponding 2-fluoro-2-iodoacetatic acid with thionyl chloride.[22] The products were isolated in low preparative yields probably due to losses caused by difficulties in purification. From this point of view, the reactions report only unoptimized yields (vide infra).

4.2. Synthesis of 2-fluoro-2-iodoacetic acid

A flask (500 mL) was charged with ethyl 2-fluoro-2-iodoacetate (60 g, 0.26 mol) and phenolphthalein (0.4 mL). A solution of 5% aq sodium hydroxide (11.4 g, 0.28 mol) was added dropwise to the reaction mixture at room temperature until a colorless residue was obtained. The mixture was acidified with concentrated HCl to pH 2. The resulting homogenous solution was extracted with ether (2×50 mL). The organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo. The residue was crystallized from methylene chloride/light petroleum to give 2-fluoro-2-iodocetic acid (8.6 g, 16%) as white needles, mp 76–79 °C. Found: C, 12.17; H, 1.13; F, 9.40. $C_2H_2O_2FI$ requires: C, 11.78; H, 0.99; F, 9.32%. ν_{max} (CCl_4) 3517, 3120, 3040, 2898, 2743, 2636, 2549, 2477, 1793, 1743, 1245, 1154, 1083, 917 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 7.20 (1H, d, *J* 51.1 Hz), 11.13 (1H, s); δ_C (75.5 MHz, $CDCl_3$) 55.9 (*J* 264 Hz), 173.2 (*J* 25 Hz); δ_F (75.4 MHz, $CDCl_3$) −162.1 (d, *J* 50.7 Hz).

4.3. 2-Fluoro-2-iodoacetic chloride

A mixture of 2-fluoro-2-iodoacetic acid (8.4 g, 41 mmol) and thionyl chloride (17 g, 0.20 mol) in methylene chloride (9 mL) was heated to reflux for 25 h. After removal of thionyl chloride and methylene chloride at 78 °C under low pressure (99 mmHg), purification of the crude product by distillation gave 2-fluoro-2-iodoacetic chloride (3.1 g, 34%) as a deep red liquid, bp 69–70 °C/95 mmHg; δ_H (300.1 MHz, $CDCl_3$) 7.26 (1H, d, *J* 51.7 Hz); δ_F (75.4 MHz, $CDCl_3$) −149.2 (d, *J* 51.8 Hz).

4.4. 1-Benzyl-3-butyl-2,4-dioxo-1,2,3,4,-tetrahydroquinolin-3-yl bromoacetate (2a)

To a solution of **1a** (1.62 g, 5.0 mmol) in benzene (15 mL) was added a solution of pyridine (830 mg, 10.5 mmol) in benzene (5 mL) and a solution of 2-bromoacetyl bromide (2.12 g, 10.5 mmol) in benzene (5 mL). The resulting mixture was stirred at room temperature for 14 h. After complete conversion of **1a** (TLC, 20% benzene/EtOAc), the precipitate was filtered off and the filtrate was evaporated to dryness in vacuo. Purification of the crude product by crystallization with xylene/methanol gave **2a** (1.45 g, 65%) as white needles, mp 142–145 °C. Found: C, 59.22; H, 4.95; N, 3.12. $C_{22}H_{22}O_4NBr$ requires: C, 59.47; H, 4.99; N, 3.15%. R_f (20% EtOAc/benzene) 0.67; ν_{max} ($CHCl_3$) 1711, 1673, 1601 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.1 Hz), 1.29 (2H, m, *J* 7.3 Hz), 1.36–1.52 (2H, m), 2.07 (2H, ddd, *J* 14.0, 9.3, 6.9 Hz), 4.05 (2H, s), 5.26 (1H, d, *J* 16.5 Hz), 5.33 (1H, d, *J* 16.5 Hz), 7.04 (1H, d, *J* 8.2 Hz), 7.14 (1H, t, *J* 7.5 Hz), 7.21–7.40 (6H, m), 7.49 (1H, dt, *J* 8.0, 1.7 Hz), 8.00 (1H, dd, *J* 8.0, 1.4 Hz); δ_C (75.5 MHz, $CDCl_3$) 14.3, 23.0, 25.2, 36.8, 25.4, 47.0, 87.5, 116.9, 124.3, 127.1, 128.3, 129.4, 129.8, 137.2, 121.1, 136.2, 142.6, 167.3, 169.7, 190.8.

4.5. {2-[(1-Benzyl-3-butyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl)oxycarbonyl]methyl}(triphenyl)phosphonium bromide (3a)

A suspension of **2a** (1.32 g, 2.97 mmol) and triphenylphosphane (857 mg, 3.27 mmol) was refluxed in benzene (10 mL) for 3 h. After 15 min, the suspension became clear and after 20 min a precipitate was formed. After cooling, the precipitate of the product was filtered off and the filtrate was refluxed for 3 h. Another portion of the crude product contained a variable quantity of butenolide **4a** (according to TLC, 20% benzene/EtOAc), which was then filtered off to give **3a** (1.29 g, 61%) as a white amorphous solid. Found: C, 67.80; H, 5.41; N, 1.77. $C_{40}H_{37}O_4NBrP$ requires: C, 67.99; H, 5.28; N, 1.98%. R_f (20% EtOAc/benzene) 0.00; ν_{max} ($CHCl_3$) 3438, 2959, 2929, 1739, 1706, 1673, 1601, 1470, 1436, 1111, 756, 691 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 0.80 (3H, t, *J* 6.6 Hz), 1.11–1.29 (4H, m), 1.79–1.96 (2H, m), 5.05 (1H, d, *J* 16.5 Hz), 5.26 (1H, d, *J* 16.5 Hz), 5.33 (1H, dd, *J* 30.2, 14.3 Hz), 5.47 (1H, dd, *J* 31.3, 16.5 Hz), 6.94–7.97 (24H, m); δ_C (75.5 MHz, $CDCl_3$) 14.2, 23.0, 25.2, 36.7, 32.4 (d, *J* 56.1 Hz), 46.8, 87.4, 116.6, 117.5, 118.7, 116.8, 124.4, 127.1, 128.3, 129.4, 129.7, 137.2, 131.0, 131.2, 136.0, 120.9, 129.1, 142.2, 164.4, 170.0, 189.8.

4.6. 5-Benzyl-3a-butyl-furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-dione (4a)

A solution of **3a** (1.25 g, 1.77 mmol) in chloroform (20 mL) was shaken with 0.5 M sodium hydroxide (7.1 mL, 3.53 mmol) in a separatory funnel for 5 min. The mixture was then set aside for 20 min. The aqueous layer was separated and extracted with chloroform (2×10 mL). The combined organic layers were washed with water (5 mL) and dried with anhydrous sodium sulfate. The solvent was then evaporated to dryness in vacuo. Purification of the crude product by crystallization with benzene/hexane gave **4a** (322 mg, 52%) as white needles, mp 172–174 °C. Found:

C, 76.63; H, 6.35; N, 3.86. $C_{22}H_{21}O_3N$ requires: C, 76.36; H, 6.09; N, 4.03%. R_f (20% EtOAc/benzene) 0.56; ν_{max} ($CHCl_3$) 3437, 3101, 2954, 2927, 1745, 1700, 1640, 1467, 1209, 775 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.1 Hz), 1.16–1.41 (4H, m), 1.68–1.82 (1H, m), 2.14–2.29 (1H, m), 4.86, 5.51 (2H, 2×d, *J* 16.2, 15.9 Hz), 6.10 (1H, s), 7.05 (1H, d, *J* 8.2 Hz), 7.12–7.45 (7H, m), 7.56 (1H, d, *J* 7.4 Hz); δ_C (75.5 MHz, $CDCl_3$) 14.3, 22.8, 25.2, 38.1, 47.3, 87.5, 117.2, 113.0, 124.8, 127.1, 127.9, 128.4, 129.8, 133.8, 118.0, 136.6, 139.5, 163.4, 168.1, 171.7.

4.7. Reaction of 1-benzyl-3-butyl-3-hydroxy-1,2,3,4-tetrahydroquinolin-2,4-dione (1a) with ethyl 2-(triphenylphosphoranylidene)acetate (products 4a and 5)

A mixture of **1a** (1.62 g, 5.0 mmol) and ethyl 2-(triphenylphosphoranylidene)acetate (1.91 g, 5.5 mmol) in xylene (15 mL) was heated to reflux for 4 h. After cooling, the mixture was purified by chromatography on silica gel (benzene and 95% benzene/EtOAc). Compound **5** was then crystallized from benzene.

4.7.1. 5-Benzyl-3a-butyl-furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-dione (4a). Yield, 9 mg (0.5%) of white amorphous solid. NMR data were identical to above-mentioned compound (see Section 4.6).

4.7.2. Ethyl (*E*)-[1-benzyl-3-butyl-3-hydroxy-2-oxo-2,3-dihydroquinoline-4(1*H*)-ylidene]acetate (5). Yield, 1.23 g (68%) of white needles, mp 72–74 °C. Found: C, 73.26; H, 6.92; N, 3.56. $C_{24}H_{27}O_4N$ requires: C, 72.95; H, 6.91; N, 3.72%. R_f (20% EtOAc/benzene) 0.82; ν_{max} ($CHCl_3$) 3363, 2978, 2953, 2868, 1714, 1669, 1628, 1600, 1466, 1179 cm^{-1} δ_H (300.1 MHz, $CDCl_3$) 0.80 (3H, t, *J* 7.1 Hz), 1.10–1.44 (4H, m), 1.24 (3H, t, *J* 7.1 Hz), 1.63 (2H, t, *J* 8.2 Hz), 4.08 (1H, br s), 4.17 (2H, q, *J* 7.1 Hz), 4.78 (1H, d, *J* 15.9 Hz), 5.52 (1H, d, *J* 16.5 Hz), 6.52 (1H, s), 6.93 (1H, d, *J* 8.2 Hz), 7.08 (1H, t, *J* 7.7 Hz), 7.16–7.41 (6H, m), 7.66 (1H, d, *J* 7.7 Hz); δ_C (75.5 MHz, $CDCl_3$) 14.3, 14.6, 23.1, 25.7, 38.8, 48.6, 61.1, 77.0, 116.4, 124.2, 126.9, 128.3, 129.7, 131.0, 131.5, 123.0, 137.0, 138.5, 167.1, 173.8.

4.8. Synthesis of quinoline-2,4-diones 6a,b: general procedure

To a mixture of **1a**,**b** (0.62 mmol) and pyridine (68.5 mg, 0.87 mmol) in methylene chloride (3 mL) was added dropwise at 0 °C acetyl chloride (2.81 mmol). After warming to room temperature, the mixture was stirred for 14 h and then diluted with methylene chloride (20 mL) and shaken with 0.1 N HCl (5 mL). The water layer was extracted with chloroform (2×10 mL), the combined extracts were washed with sodium hydrogen carbonate solution (2 mL) and water (2 mL) and dried over magnesium sulfate. Methylene chloride was then removed in vacuo and the products **6a**,**b** were crystallized (the solvent is indicated for each compound).

4.8.1. 1-Benzyl-3-butyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl acetate (6a). Yield, 160 mg (73%) as white needles (methanol), mp 122–125 °C. Found: C, 72.74; H, 6.65; N, 3.51. $C_{21}H_{23}O_4N$ requires: C, 72.51; H, 6.36; N, 3.83%. R_f (20% EtOAc/benzene) 0.80; ν_{max} ($CHCl_3$) 3027, 2962, 2932, 2876, 1744, 1712, 1679, 1602, 1469, 1374, 1247, 700 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.1 Hz), 1.18–1.52 (4H, m), 1.91–2.17 (2H, ddd, *J* 19.8, 8.3, 7.2 Hz), 2.25 (3H, s), 5.22 (1H, d, *J* 16.5 Hz), 5.38 (1H, d, *J* 15.9 Hz), 7.03 (1H, d, *J* 8.8 Hz), 7.13 (1H, t, *J* 7.5 Hz), 7.20–7.38 (5H, m), 7.47 (1H, t, *J* 7.7 Hz), 8.01 (1H, d, *J* 7.7 Hz); δ_C (75.5 MHz, $CDCl_3$) 14.3, 20.9, 23.1, 25.3, 36.7, 46.9, 84.6, 116.8, 124.1, 127.0, 128.2, 129.3, 129.7, 136.9, 121.2, 136.4, 142.6, 170.5, 171.2, 191.7.

4.8.2. 1-Methyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinolin-3-yl acetate (6b). Yield, 157 mg (82%) as white needles (benzene/methanol), mp 149–152 °C. Found: C, 69.63; H, 4.94; N, 4.23. $C_{18}H_{15}O_4N$ requires: C, 69.81; H, 4.89; N, 4.63%. R_f (20% EtOAc/benzene) 0.72; ν_{max} ($CHCl_3$) 3025, 1742, 1715, 1679, 1605, 1474, 1359, 1247, 685 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 2.30 (3H, s), 3.57 (3H, s), 7.18 (1H, t, *J* 7.4 Hz), 7.20 (1H, d, *J* 8.8 Hz), 7.28–7.49 (5H, s), 7.64 (1H, t, *J* 8.0 Hz), 7.99 (1H, d, *J* 7.7 Hz); δ_C (75.5 MHz, $CDCl_3$) 21.0, 30.8, 85.6, 116.0, 121.3, 124.3, 127.4, 129.6, 129.8, 130.6, 133.2, 137.3, 143.4, 169.0, 171.4, 190.0.

4.9. The stability study of lithium salt of ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (12) using ^{19}F NMR at temperature gradient

A flask (25 mL) was charged with ethyl 2-(diethoxyphosporyl)-2-fluoroacetate (150 mg, 0.62 mmol) in dry tetrahydrofuran (3 mL) and cooled under argon to −78 °C. A solution of *n*-butyllithium in hexane (2.5 M, 0.71 mmol) was added dropwise to the flask with stirring. A NMR tube was charged with dry tetrahydrofuran-d_8 (200 μL) and cooled under argon to −78 °C. After 20 min of stirring, a sample of resulting reaction mixture including a lithium-fluorophosphonate salt was rapidly withdrawn by a pre-cooled syringe (300 μL), added to a cooled NMR tube and the ^{19}F NMR spectrum was taken while cooling. The reaction temperature was stepwise increased from −70 to +35 °C and the NMR analysis was carried out. δ_F (75.4 MHz, $CDCl_3$) −229.1 (1F, br s at −70 °C). The content of the compounds in the reaction mixture was determined by ^{19}F NMR and are as follows [time (min)/temperature (°C)/**13** (rel %)/**12** (rel %)]: 20/−70/0/100; 31/−35/0/100; 42/−15/7/93; 67/5/10/90; 85/25/11/89; 100/35/11/89.

4.10. Wittig–Horner reaction of quinoline-2,4-diones 6a,b with lithium salt of ethyl 2-(diethoxyphosphoryl)-2-fluoroacetic acid (12) using ^{19}F NMR at temperature gradient: general procedure

A NMR tube was charged with ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (25 mg, 105 μmol) in dry tetrahydrofuran (300 μL) and tetrahydrofuran-d_8 (200 μL) and cooled under nitrogen to −78 °C. A solution of *n*-butyllithium in hexane (2.5 M, 172 μmol) was added dropwise to the flask with stirring. After 20 min of stirring, the ^{19}F NMR spectrum was taken while cooling. The quinoline-2,4-dione **1a** or **1b** (100 μmol) was dissolved in tetrahydrofuran and the resulting solution was added to the cooling mixture. The reaction temperature was stepwise increased from −70 to +35 °C and the NMR analysis was carried out.

4.10.1. 5-Benzyl-3a-butyl-1-fluorofuro[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-dione (8a). The conversion of **1a** to butenolide **8a** was approximately ~2% at 25–35 °C. After 188 min, the mixture contained only the decomposed Wittig–Horner reagent. Butenolide **8a** was characterized in the mixture by ^{19}F NMR. δ_F (75.4 MHz, $CDCl_3$) −144.1 (s); *m*/*z* (EI) 365 (25%, M^+). HRMS (EI): M^+, found 365.1419; $C_{22}H_{20}FNO_3$ requires 365.1421. The content of the compounds in the reaction mixture was determined by ^{19}F NMR and are as follows [time (min)/temperature (°C)/**8a** (rel %)/**12** (rel %)]: 24/−70 to 50/0/100; 70/−50/0/68; 108/−30/0/49; 143/10/0/44; 188/35/~2/36.

4.10.2. 1-Fluoro-5-methyl-3a-phenyl-furo[2,3-*c*]quinoline-2,4(3a*H*,5*H*)-dione (8b). The conversion of **1b** to butenolide **8b** was approximately 16% at +35 °C. After 166 min, the reaction contained only the decomposed Wittig–Horner reagent. Butenolide **6b** was characterized in the mixture by ^{19}F NMR. δ_F (75.4 MHz, $CDCl_3$) −148.1 (s); *m*/*z* (EI) 309 (11%, M^+); HRMS (EI): M^+, found 309.0820; $C_{18}H_{12}FNO_3$ requires 309.0801. The content of the compounds in the reaction mixture were determined by ^{19}F NMR and were as follows [time (min)/temperature (°C)/**8b** (rel %)/**12** (rel %)]: 300/−70 to 10/0/100; 314/10/0/100; 331/35/0.4/95; 366/35/16/43; 496/35/16/0.

4.11. 1-Benzyl-3-butyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl 2-fluoro-2-iodoacetate (9a)

To a mixture of **1a** (300 mg, 0.93 mmol) and pyridine (92 mg, 1.12 mmol) in methylene chloride (5 mL) was added dropwise at −20 °C fluoroiodoacetyl chloride (329 mg, 1.48 mmol). After warming to room temperature, the mixture was stirred for 14 h. Methylene chloride was then removed in vacuo. Purification of the crude product by chromatography on neutral aluminum oxide (20% EtOAc/benzene) gave **9a** (227 mg, 48%) as a white amorphous solid. Found: C, 51.52; H, 4.22; N, 24.78. $C_{22}H_{21}FINO_4$ requires: C, 51.88; H, 4.16; N, 24.92%. R_f (20% EtOAc/benzene) 0.82; δ_H (300.1 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.1 Hz), 1.29 (2H, m, *J* 7.3 Hz), 1.42 (2H, pent, *J* 7.8 Hz), 1.97–2.23 (2H, m), 5.32 (1H, d, *J* 16.5 Hz), 5.36 (1H, d, *J* 16.5 Hz), 7.06 (1H, dd, *J* 8.2, 2.2 Hz), 7.16 (1H, dt, *J* 7.7, 2.2 Hz), 7.20–7.40 (5H, m), 7.37 (1H, d, *J* 51.1 Hz), 7.51 (1H, m), 8.0 (1H, dd, *J* 7.7, 1.7 Hz); δ_C (75.5 MHz, $CDCl_3$) 14.3, 23.0, 25.3, 36.9, 47.1, 56.4 (*J* 263.4 Hz), 86.4, 116.9, 124.5, 127.1, 128.4, 129.5, 129.8, 137.3, 121.0, 136.1, 142.6, 165.9 (*J* 28.3 Hz), 169.0, 190.6; δ_F (376.5 MHz, $CDCl_3$) −162.50 (d, *J* 50.7 Hz); *m*/*z* (EI) 306 (52; M^+−CHFICOO), 277 (11), 266 (15), 234 (5), 208 (7), 146 (5), 103 (2), 91 (100), 77 (5), 67 (16%).

4.12. Synthesis of quinoline-2,4-diones 14a–16d: general procedure

To a mixture of **1a–d** and pyridine in methylene chloride (5 mL) was added dropwise at 0 °C acyl agent (see Sections 4.12.1–4.12.9). After warming to room temperature, the mixture was stirred for 14 h. Methylene chloride was then removed (rotary evaporator) and the crude product was purified by flash chromatography on neutral aluminum oxide (20% EtOAc/benzene, see Sections 4.12.4–4.12.9) or used in the Perkow reaction without further purification (see Sections 4.12.1–4.12.3).

4.12.1. 1-Benzyl-3-butyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl 2,2,2-trifluoroacetate (14a). The reaction of **1a** (100 mg, 0.70 mmol) with pyridine (112 mg, 1.42 mmol) and trifluoroacetic anhydride (300 mg, 1.42 mmol) afforded after evaporation of solvents a residue containing the crude unstable compound **14a** in quantitative yield (according to TLC, 20% EtOAc/benzene). The product was used in the Perkow reaction (see Section 4.13.4) without further purification. R_f (20% EtOAc/benzene) 0.74; δ_F (376.5 MHz, $CDCl_3$) −75.07 (s); *m*/*z* (EI) 419 (4, M^+), 305 (13), 234 (4), 214 (5), 180 (4), 91 (100), 65 (9%).

4.12.2. 1-Methyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinolin-3-yl 2,2,2-trifluoroacetate (14b). The reaction of **1b** (100 mg, 0.37 mmol) with pyridine (112 mg, 1.42 mmol) and trifluoroacetic anhydride (300 mg, 1.42 mmol) afforded after evaporation of solvents a residue containing the crude unstable product **14b** in quantitative yield (according to TLC, 20% EtOAc/benzene). The product was used in the Perkow reaction (see Section 4.13.5) without further purification. R_f (20% EtOAc/benzene) 0.75; δ_F (376.5 MHz, $CDCl_3$) −75.17 (s); *m*/*z* (FAB) 364 (60%, MH^+).

4.12.3. 3-Methyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydroquinolin-3-yl 2,2,2-trifluoroacetate (14c). The reaction of **1c** (100 mg, 0.37 mmol) with pyridine (112 mg, 1.42 mmol) and trifluoroacetic anhydride (300 mg, 1.42 mmol) afforded after evaporation of solvents a residue containing the crude unstable product **14c** in quantitative yield (according to TLC, 20% EtOAc/benzene). The product was used in the Perkow reaction (see Section 4.13.6) without further purification. R_f (20% EtOAc/benzene) 0.79; δ_F (376.5 MHz, $CDCl_3$) −75.10 (s); *m*/*z* (FAB) 364 (22%, MH^+).

4.12.4. 1-Benzyl-3-butyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl 2,3,3-trifluoro-2,3-dichloropropanoate (15a). The reaction of **1a** (100 mg, 0.31 mmol) with pyridine (293 mg, 3.60 mmol) and 2,3,3-trifluoro-2,3-dichloropropanoyl chloride (782 mg, 3.63 mmol) afforded ester **15a** (123 mg, 79%) as a slightly yellow oil. Found: C, 55.29; H, 4.31; N, 2.88. $C_{23}H_{20}Cl_2F_3NO_4$ requires: C, 55.00; H, 4.01; N, 2.79%. R_f (20% EtOAc/benzene) 0.91; δ_H (300.1 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.1 Hz), 1.31 (2H, m, *J* 7.1 Hz), 1.44 (2H, m), 2.04–2.27 (2H, m), 5.31 (1H, s), 7.08 (1H, d, *J* 8.2 Hz), 7.17 (1H, t, *J* 7.7 Hz), 7.22–7.36 (5H, m), 7.52 (1H, t, *J* 7.9 Hz), 8.00 (1H, d, *J* 7.7 Hz); δ_C (75.5 MHz, $CDCl_3$) 14.3, 22.0, 24.6, 36.7, 47.1, 86.4, 98.7–103.0 (m), 116.9, 119.8–128.4 (m), 121.0, 124.3, 127.1, 128.2, 129.4, 129.8, 137.1, 121.0, 136.2, 142.6, 165.5 (*J* 28.1 Hz), 170.0, 191.6. δ_F (376.5 MHz, $CDCl_3$) 2×diastereoisomers, ds_1 (50% rel), ds_2 (50% rel): −64.3, −66.6 (2F, ds_1, 2×dd, *J* 171.2, 6.6, 12.7 Hz), −64.3, −66.6 (2F, ds_2, 2×dd, *J* 171.2, 6.6, 12.7 Hz), −72.8 (2F, ds_1+ds_2, t, *J* 9.3 Hz); *m*/*z* (EI) 501 (2, M^+), 305 (15), 262 (7), 214 (8), 146 (7), 91 (100), 57 (10%); HRMS (EI): M^+, found 501.0735; $C_{23}H_{20}Cl_2F_3NO_4$ requires 501.0721.

4.12.5. 1-Methyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinolin-3-yl 2,3,3-trifluoro-2,3-dichloropropanoate (15b). The reaction of **1b** (100 mg, 0.37 mmol) with pyridine (293 mg, 3.60 mmol) and 2,3,3-trifluoro-2,3-dichloropropanoyl chloride (775 mg, 3.60 mmol) afforded the crude ester **15b** (162 mg, 98%) as a slightly yellow oil.

Found: C, 51.33; H, 2.98; N, 3.38. $C_{19}H_{12}Cl_2F_3NO_4$ requires: C, 51.14; H, 2.71; N, 3.14%. R_f (20% EtOAc/benzene) 0.88; δ_H (300.1 MHz, $CDCl_3$) 3.57 (3H, d, *J* 4.4 Hz), 7.19 (2H, m), 7.40 (5H, m), 7.63 (1H, t, *J* 7.7 Hz), 7.98 (1H, d, *J* 6.6 Hz); δ_C (75.5 MHz, $CDCl_3$) 30.8, 84.0, 98.7–103.0 (m), 115.8, 119.7–128.8 (m), 121.3, 124.4, 127.4, 129.7, 129.8, 130.6, 133.2, 134.0–140.5 (m), 143.2, 164.5 (*J* 28.5 Hz), 171.4, 191.3; δ_F (376.5 MHz, $CDCl_3$) 2× diastereoisomers, ds_1 (34% rel), ds_2 (66% rel): −64.2, −66.6 (2F, 2×dd, ds_1, *J* 171.3, 9.2, 11.5 Hz), −64.3, −66.6 (2F, 2×dd, ds_2, *J* 171.3, 7.1, 11.3 Hz), −72.8 (2F, ds_1+ds_2, t, *J* 9.6 Hz); *m*/*z* (EI) 445 (7, M^+), 266 (78), 250 (10), 222 (13), 151 (5), 105 (100), 77 (43), 51 (10%); HRMS (EI): M^+, found 445.0089; $C_{19}H_{12}Cl_2F_3NO_4$ requires 445.0095.

4.12.6. 1-Benzyl-3-butyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl 2,5-bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoate (16a). The reaction of **1a** (100 mg, 0.31 mmol) with pyridine (21.5 mg; 0.27 mmol) and 2,5-bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoyl fluoride (164 mg, 0.33 mmol) afforded **16a** (245 mg, ~100%) as a slightly yellow oil. Found: C, 43.23; H, 2.38; N, 1.68. $C_{29}H_{20}F_{17}NO_6$ requires: C, 43.46; H, 2.51; N, 1.75%. R_f (20% EtOAc/benzene) 0.93; δ_H (300.1 MHz, $CDCl_3$) 0.87 (3H, t, *J* 7.1 Hz), 1.29 (2H, m), 1.43 (2H, m), 2.14 (2H, m), 5.30 (2H, s), 7.07 (1H, m), 7.17 (1H, t, *J* 7.7 Hz), 7.22–7.38 (5H, m), 7.52 (1H, t, *J* 8.2), 7.98 (1H, m); δ_C (75.5 MHz, $CDCl_3$) 14.1, 22.4, 24.9, 40.9, 46.9, 82.9, 99.6–124.7 (m), 123.9, 126.3, 126.7, 127.7, 128.1, 128.3, 129.0, 134.0, 136.1, 141.9, 142.5, 144.4, 162.5 (*J* 28.1 Hz), 172.8, 193.1; δ_F (376.5 MHz, $CDCl_3$) 2×diastereoisomers, ds_1 (50% rel), ds_2 (50% rel): −79.7 (4F, ds_1+ds_2, m), −80.4 (6F, ds_1+ds_2, m), −81.8 (6F, ds_1+ds_2, m), −82.4 (6F, ds_1+ds_2, m), −83.4 (4F, ds_1+ds_2, m), −130.0 (4F, ds_1+ds_2, s), −132.9 (1F, ds_1, dd, *J* 20.3 Hz), −133.1 (1F, ds_2, m), −145.1 (1F, ds_1, t, *J* 20.9 Hz), −145.5 (1F, ds_2, m); *m*/*z* (EI) ds_1 306 (19, $M^+-C_3F_7CF(CF_3)CF_2OCF(CF_3)CO_2$), 262 (8, CF_3CFO^+-CF_2COCF_3), 234 (5, $CF_3CF_2O^+CF_2CF_3$), 214 (4), 180 (3), 169 (13, $C_3F_7^+$), 119 (3), 91 (100), 69 (16, CF_3^+), 41 (5); ds_2 306 (29, $M^+-C_3F_7CF(CF_3)CF_2OCF(CF_3)COO$), 262 (11, $CF_3CFO^+CF_2C(O)CF_3$), 234 (6, $CF_3CF_2O^+CF_2CF_3$), 214 (8), 180 (3), 169 (15, $C_3F_7^+$), 146 (6), 119 (4), 91 (100), 69 (15, CF_3^+), 41 (5); HRMS (EI): ds_1 $M^+-C_3F_7CF(CF_3)$-$CF_2OCF(CF_3)COO$, found 306.1472; $C_{20}H_{20}NO_2$ requires 306.1490; ds_2 $M^+-C_3F_7CF(CF_3)CF_2OCF(CF_3)COO$, found 306.1480; $C_{20}H_{20}NO_2$ requires 306.1490.

4.12.7. 1-Methyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinolin-3-yl 2,5-bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoate (16b). The reaction of **1b** (100 mg, 0.37 mmol) with pyridine (29.3 mg, 0.37 mmol) and 2,5-bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoyl fluoride (224 mg, 0.45 mmol) afforded **16b** (278 mg, ~100%) as a slightly yellow oil. Found: C, 40.51; H, 1.40; N, 1.62. $C_{25}H_{12}F_{17}NO_6$ requires: C, 40.29; H, 1.62; N, 1.88%. R_f (17% EtOAc/benzene) 0.93; δ_H (300.1 MHz, $CDCl_3$) 3.57 (3H, d, *J* 4.4 Hz), 7.19 (2H, m), 7.40 (5H, m), 7.63 (1H, t, *J* 7.7 Hz), 7.97 (1H, t, *J* 7.7 Hz); δ_C (75.5 MHz, $CDCl_3$) 30.8, 83.5, 115.5, 100.0–125.1 (m), 124.4, 126.0, 126.9, 128.8, 129.4, 129.7, 136.7, 138.2, 142.7, 143.0, 144.5, 163.0 (*J* 28.3 Hz), 171.4, 193.0; δ_F (376.5 MHz, $CDCl_3$) 2×diastereoisomers, ds_1 (50% rel), ds_2 (50% rel): −79.7 (2F, ds_1+ds_2, m, *J* 150.6 Hz), −80.4 (6F, ds_1+ds_2, m), −81.9 (6F, ds_1+ds_2, m), −82.4 (6F, ds_1+ds_2, m, *J* 15.4 Hz), −82.9 (2F, ds_1, 2×d, *J* 150.6 Hz), −83.6 (2F ds_2, 2×d, *J* 150.6 Hz), −130.0 (6F, ds_1+ds_2, 2×s), −132.7 (1F, ds_1, dd, *J* 20.3 Hz), 132.9 (1F, ds_2, m), −145.1 (1F, ds_1, t, *J* 21.8 Hz), −145.5 (1F, ds_2, dd, *J* 21.1 Hz); *m*/*z* (EI) 250 (31, $M^+-C_3F_7CF$-$(CF_3)CF_2OCF(CF_3)COO$), 266 (100), 222 (23), 194 (3), 169 (28, $C_3F_7^+$), 152 (4), 125 (4), 105 (85, $PhCO^+$), 77 (28), 69 (32, CF_3^+), 51 (7%, CHF_2^+); HRMS (EI): ds_1 $M^+-C_3F_7CF(CF_3)CF_2OCF(CF_3)COO$, found 250.0855; $C_{16}H_{12}NO_2$ requires 250.0870; ds_2 $M^+-C_3F_7CF(CF_3)$-$CF_2OCF(CF_3)COO$, found 250.0862; $C_{16}H_{12}NO_2$ requires 250.0870.

4.12.8. 3-Methyl-2,4-dioxo-1-phenyl-1,2,3,4-tetrahydroquinolin-3-yl 2,5-bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoate (16c). The reaction of **1c** (100 mg, 0.37 mmol) with pyridine (108 mg, 1.41 mmol) and 2,5-bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoyl fluoride (661 mg, 1.33 mmol) afforded **16c** (268 mg, 96%) as a slightly yellow oil. Found: C, 40.42; H, 1.51; N, 1.77. $C_{25}H_{12}F_{17}NO_6$ requires: C, 40.29; H, 1.62; N, 1.88%. R_f (20% EtOAc/benzene) 0.88; δ_H (300.1 MHz, $CDCl_3$) 1.92 (3H, s), 6.51 (3H, d, *J* 8.5 Hz), 7.20 (1H, t, *J* 7.6 Hz), 7.26 (2H, m), 7.46 (1H, t, *J* 8.5 Hz), 7.56 (3H, m), 8.04 (1H, ddd, *J* 7.6, 3.5, 1.4 Hz); δ_C (75.5 MHz, $CDCl_3$) 16.8, 83.1, 100.0–124.8 (m), 116.4, 120.7, 123.9, 124.2, 129.4, 129.5, 130.6, 130.8, 136.5, 139.9, 163.0 (*J* 28.2 Hz), 172.4, 193.2; δ_F (376.5 MHz, $CDCl_3$) 2×diastereoisomers, ds_1 (50% rel), ds_2 (50% rel) −79.7 (4F, ds_1+ds_2, m, *J* 150.6 Hz); −80.4 (6F, ds_1+ds_2, m), −81.9 (6F, ds_1+ds_2, m), −82.4 (6F, ds_1+ds_2, m, *J* 15.4 Hz), −82.9 (2F, ds_1, 2×d, *J* 150.6 Hz), −83.6 (2F, ds_2, 2×d, *J* 150.6 Hz), −130.0 (4F, ds_1+ds_2, 2×s), −133.9 (1F, ds_1, dd, *J* 19.9 Hz), 132.9 (1F, ds_2, m), −145.5 (1F, ds_1, q, *J* 19.9 Hz), −145.8 (2F, ds_1+ds_2, q, *J* 21.7 Hz); *m*/*z* (FAB) 746 (3, MH^+); HRMS (FAB): MH^+, found 746.0038; $C_{25}H_{13}F_{17}NO_6$ requires 746.0047.

4.12.9. 3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl 2,5-bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoate (16d). The reaction of **1d** (104 mg, 0.37 mmol) with pyridine (108 mg, 1.41 mmol) and 2,5-bis(trifluoromethyl)-2,4,4,5,7,7,8,8,9,9,9-undecafluoro-3,6-dioxanonanoyl fluoride (759 mg, 1.52 mmol) afforded **16d** (237 mg, 84%) as a slightly yellow oil. Found: C, 41.22; H, 1.92; N, 1.98. $C_{26}H_{14}F_{17}NO_6$ requires C, 41.12; H, 1.86; N, 1.84%. R_f (20% EtOAc/benzene) 0.90; δ_H (300.1 MHz, $CDCl_3$) 3.33 (2H, d, *J* 6.7 Hz), 3.40 (3H, s), 6.90 (3H, m), 7.12 (4H, m), 7.53 (1H, t, *J* 8.2 Hz), 7.89 (1H, t, *J* 7.3 Hz); δ_F (376.5 MHz, $CDCl_3$) 2×diastereoisomers, ds_1 (50% rel), ds_2 (50% rel): −79.7 (4F, ds_1+ds_2, m, *J* 150.6 Hz), −80.4 (6F, ds_1+ds_2, m), −81.9 (6F, ds_1+ds_2, m), −82.4 (6F, ds_1+ds_2, m, *J* 15.4 Hz), −82.9 (2F, ds_1, 2×d, *J* 150.6 Hz), −83.6 (2F, ds_2, 2×d, *J* 150.6 Hz), −130.0 (4F, ds_1+ds_2, 2×s), −132.7 (1F, ds_1, dd, *J* 20.3 Hz), 132.9 (1F, ds_2, m), −145.1 (1F, t, ds_1, *J* 21.8 Hz), −145.5 (1F, ds_2, dd, *J* 21.1 Hz); *m*/*z* (FAB) 760 (3%, MH^+); HRMS (FAB): MH^+, found 760.0622; $C_{26}H_{15}F_{17}NO_6$ requires 760.0630.

4.13. Reactions of quinoline-2,4-diones 6a,b, 9a, and 14a–16d with triethyl phosphite: general procedure

A mixture of **6a**,**b**, **9a**, and **14a**–**16d** and triethyl phosphite in toluene was vigorously refluxed until the reaction was completed. After removal of solvents, the residue was purified in the below-mentioned systems (vide infra) and the obtained products **17a**,**b** and **18** were crystallized from acetone/hexane.

4.13.1. Reaction of 1-benzyl-3-butyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-yl acetate (6a) with triethyl phosphite. A mixture of **6a** (65 mg, 0.16 mmol) and triethyl phosphite (278 mg, 1.60 mmol) in toluene (2 mL) was vigorously heated to reflux for 16 h; no product was formed (according to TLC, 20% EtOAc/benzene).

4.13.2. Reaction of 1-methyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinolin-3-yl acetate (6b) with triethyl phosphite. A mixture of **6b** (100 mg, 0.32 mmol) in toluene (2 mL) and triethyl phosphite (278 mg, 1.60 mmol) was vigorously heated to reflux for 10 h; no product was formed (according to TLC, 20% EtOAc/benzene).

4.13.3. Reaction of quinoline-2,4-dione 9a with triethyl phosphite: (1-benzyl-3-butyl-2-oxo-1,2-dihydroquinolin-4-yl)diethyl phosphate (17a). A mixture of **9a** (168 mg, 0.34 mmol) and triethyl phosphite (562 mg, 3.38 mmol) in toluene (5 mL) was vigorously heated to reflux for 7 h. After removal of the solvents, the residue was purified by chromatography on neutral aluminum oxide (20% EtOAc/benzene). The obtained product **17a** (102 mg, 68%) was crystallized from acetone/hexane for analytical purposes to give white needles (61 mg, 41%), mp 94–97 °C. Found: C, 65.00; H, 6.82; N, 3.06. $C_{24}H_{30}O_5NP$ requires: C, 65.00; H, 6.81; N, 3.16%. R_f (20% EtOAc/benzene) 0.31; ν_{max} ($CDCl_3$) 3010, 2961, 1643, 1600, 1461, 1050, 1031, 967, 902 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.1 Hz), 1.36 (6H, dt, *J* 7.1, 1.1 Hz), 1.45 (2H, m, *J* 7.4 Hz), 1.62 (2H, pent, *J* 7.7 Hz), 2.85 (2H, t, *J* 8.0 Hz), 4,26 (4H, m), 5.55 (2H, br s), 7.16–7.34 (7H, m), 7.41 (1H, ddd, *J* 7.1, 1.7 Hz), 8.00 (1H, dd, *J* 8, 1.4 Hz); δ_C (75.5 MHz, $CDCl_3$) 13.9, 16.1 (*J* 7 Hz), 23.0, 25.5, 30.1, 46.4, 65.0 (*J* 6 Hz), 114.6, 117.3, 122.0, 123.9 (*J* 5 Hz), 124.1, 126.5, 127.2, 128.7, 130.3, 136.3, 137.9, 151.3 (*J* 9 Hz), 163.3; δ_P (202.5 MHz, $CDCl_3$) −5.19 (pent, *J* 15.1 Hz); *m*/*z* (EI) 443 (3, M^+), 414 (1), 401 (7), 289 (8), 282 (4), 254 (9), 198 (13), 91 (100), 77 (3), 65 (8), 43 (2%).

4.13.4. Reaction of quinoline-2,4-dione 14a with triethyl phosphite: (1-benzyl-3-butyl-2-oxo-1,2-dihydroquinolin-4-yl)diethyl phosphate (17a). A mixture of **14a** (see Section 4.12.1) and triethyl phosphite (562 mg, 3.38 mmol) in toluene (6 mL) was heated to reflux for 3 days. After the removal of the solvents, the residue was purified by chromatography on neutral aluminum (20% EtOAc/benzene). The obtained product **17a** (43 mg, 36%) was crystallized for analytical purposes with acetone/hexane to give (31 mg, 26%) of white crystals. NMR spectra were identical to above-mentioned compound (see Section 4.13.3).

4.13.5. Reaction of quinoline-2,4-dione 14b with triethyl phosphite: (1-methyl-2-oxo-3-phenyl-1,2-dihydroquinolin-4-yl)diethyl phosphate (17b). A mixture of **14b** (see Section 4.12.2) and triethyl phosphite (562 mg, 3.38 mmol) in toluene (5 mL) was heated to reflux for 9 h. After removal of the solvents, the residue was purified by chromatography on neutral aluminum oxide (17–50% EtOAc/benzene). The obtained product **17b** (55 mg, 36%) was crystallized for analytical purposes from acetone/hexane to give white needles (32 mg, 28%), mp 97–99 °C. Found: C, 62.05; H, 5.83; N, 3.53. $C_{20}H_{22}O_5NP$ requires: C, 62.04; H, 5.73; N, 3.73%. R_f (50% EtOAc/benzene) 0.25; ν_{max} ($CDCl_3$) 3011, 1639, 1597, 1464, 1042, 970, 901 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 1.14 (3H, dt, *J* 7.1, 1.1 Hz), 3.64, 3.80 (4H, 2×m), 3.76 (3H, s), 7.29–7.51 (7H, m), 7.63 (1H, dt, *J* 7.2, 1.1 Hz), 8.11 (1H, dd, *J* 8.0, 1.4 Hz); δ_C (75.5 MHz, $CDCl_3$) 15.9 (*J* 7 Hz), 30.0, 64.4 (*J* 6 Hz), 113.9, 117.1, 122.2, 123.4, 124.8, 127.9, 130.9, 131.3, 132.4, 139.2, 151.4 (*J* 7 Hz), 162.6; δ_P (202.5 MHz, $CDCl_3$) −5.72 (pent, *J* 14.1 Hz); *m*/*z* (EI) 387 (100, M^+), 358 (16), 330 (14), 312 (6), 260 (34), 250 (68), 205 (37), 178 (9), 165 (18), 134 (24), 104 (16), 81 (48), 77 (32), 51 (9%).

4.13.6. Reaction of quinoline-2,4-dione 14c with triethyl phosphite: (3-methyl-2-oxo-1-phenyl-1,2-dihydroquinolin-4-yl)diethyl phosphate (17c). A mixture of **14c** (see Section 4.12.3) and triethyl phosphite (562 mg, 3.38 mmol) in toluene (5 mL) was heated to reflux for 2 h. After removal of the solvents, the residue was purified by chromatography on neutral aluminum oxide (20–50% EtOAc/benzene) to give **17c** (45 mg, 31%). NMR spectra were identical to below-mentioned compound (see Section 4.13.11).

4.13.7. Reaction of quinoline-2,4-dione 15a with triethyl phosphite. A mixture of **15a** (100 mg, 0.20 mmol) and triethyl phosphite (562 mg, 3.38 mmol) in toluene (3 mL) was heated to reflux for 38 h; no product was formed (according to TLC, 20% EtOAc/benzene).

4.13.8. Reaction of quinoline-2,4-dione 15b with triethyl phosphite: 4-ethoxy-1-methyl-3-phenylquinolin-2(1*H*)-one (18). A mixture of **15b** (162 mg, 0.37 mmol) and triethyl phosphite (1.91 g, 11.56 mmol) in toluene (4 mL) was heated to reflux for 14 h. After removal of the solvents, the residue was purified by chromatography on neutral aluminum oxide (20% EtOAc/benzene). The obtained product **18** (28 mg, 27%) was crystallized for analytical purposes from acetone/hexane to give white needles (10 mg, 10%), mp 98–101 °C. Found: C, 77.19; H, 6.20; N, 5.01. $C_{18}H_{17}O_2N$ requires: C, 77.40; H, 6.13; N, 5.30%. R_f (17% EtOAc/benzene) 0.27; ν_{max} ($CDCl_3$) 3010, 1624, 1592, 1463, 699 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 1.16 (3H, t, *J* 7.1 Hz), 3.64 (2H, q, *J* 7.1 Hz), 3.75 (3H, s), 7.24–7.55 (7H, m), 7.60 (1H, m, *J* 7.2, 1.7 Hz), 8.03 (1H, dd, *J* 8.0, 1.4 Hz); δ_C (75.5 MHz, $CDCl_3$) 15.4, 29.8, 69.2, 113.8, 121.8, 124.2, 127.6, 127.9, 130.6, 130.7, 119.7, 118.7, 133.7, 139.3, 159.6, 163.3; *m*/*z* (EI) 279 (97, M^+), 264 (28), 250 (100), 234 (40), 222 (21), 208 (9), 194 (12), 178 (8), 165 (16), 152 (15), 134 (39), 104 (16), 91 (13), 77 (37), 63 (13%).

4.13.9. Reaction of quinoline-2,4-dione 16a with triethyl phosphite: (1-benzyl-3-butyl-2-oxo-1,2-dihydroquinolin-4-yl)diethyl phosphate (17a). A mixture of **16a** (247 mg, 0.31 mmol) and triethyl phosphite (1.91 g, 11.56 mmol) in toluene (4 mL) was heated to reflux for 14 h. After removal

of the solvents, the residue was purified by chromatography on neutral aluminum oxide (17–50% EtOAc/benzene) to give **17a** (26 mg, 18%) as a white solid. NMR spectra were identical to the above-mentioned compound (see Section 4.13.3).

4.13.10. Reaction of quinoline-2,4-dione 16b with triethyl phosphite: 4-ethoxy-1-methyl-3-phenylquinolin-2(1*H*)-one (18). A mixture of **16b** (245 mg, 0.37 mmol) and triethyl phosphite (1.91 g, 11.56 mmol) in toluene (5 mL) was refluxed for 14 h. After removal of the solvents, the residue was purified by chromatography on neutral aluminum oxide (17% EtOAc/benzene) to give **18** (11 mg, 11%) as a white solid. NMR spectra were identical to the above-mentioned compound (see Section 4.13.8).

4.13.11. Reaction of quinoline-2,4-dione 16c with triethyl phosphite: (3-methyl-2-oxo-1-phenyl-1,2-dihydroquinolin-4-yl) diethyl phosphate (17c). A mixture of **16c** (235 mg, 0.32 mmol) and triethyl phosphite (1.91 g, 11.56 mmol) in toluene (10 mL) was heated to reflux for 2 h. After removal of the solvents, the residue was purified by chromatography on neutral aluminum oxide (17–20% EtOAc/benzene) to give **17c** (25 mg, 21%) as a white amorphous solid, mp 94–97 °C. Found: C, 61.63; H, 5.77; N, 3.45. $C_{20}H_{22}NO_5P$ requires: C, 62.01; H, 5.72; N, 3.62%. R_f (20% EtOAc/benzene) 0.36; ν_{max} ($CDCl_3$) 3011, 1645, 1603, 1459, 1048, 1034, 1034, 972, 871, 699 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.1 Hz), 2.31 (3H, d, *J* 2.1 Hz), 4.30 (2H, m), 6.66 (1H, d, *J* 8.2 Hz), 7.27 (4H, m), 7.55 (3H, m), 7.99 (1H, d, *J* 7.7 Hz); δ_C (75.5 MHz, $CDCl_3$) 12.0 (*J* 1 Hz), 16.8 (*J* 7 Hz), 65.8 (*J* 6 Hz), 116.3, 122.9, 124.2, 129.47, 127.51, 130.6, 130.8, 117.4 (*J* 2 Hz), 120.7 (*J* 5 Hz), 138.5, 140.0, 152.3 (*J* 9 Hz), 164.2; δ_P (202.5 MHz, $CDCl_3$) −4.89 (pent, *J* 7.3 Hz); *m/z* (FAB) 388.0 (100%, MH^+).

4.13.12. Reaction of quinoline-2,4-dione 16d with triethyl phosphite: (3-benzyl-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)diethyl phosphate (17d). A mixture of **16d** (230 mg, 0.30 mmol) and triethyl phosphite (1.91 g, 11.56 mmol) in toluene (10 mL) was heated to reflux for 2 h. After removal of the solvents, the residue was purified by preparative TLC (S1, 50% EtOAc/toluene) to give **17d** (65 mg, 54%) as a white solid, mp 65–67 °C. Found: C, 62.65; H, 6.00; N, 3.51. $C_{21}H_{24}NO_5P$ requires: C, 62.84; H, 6.03; N, 3.49%. R_f (50% EtOAc/toluene) 0.21; ν_{max} ($CHCl_3$) 3011, 1643, 1600, 1466, 1050, 1034, 965, 904, 700, 629 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.3 Hz), 3.69 (3H, s), 4.20 (2H, s), 4.22 (2H, m), 7.13 (1H, t, *J* 7.3 Hz), 7.18–7.40 (6H, m), 7.55 (1H, t, *J* 7.6 Hz), 8.02 (1H, d, *J* 7.9 Hz); δ_C (75.5 MHz, $CDCl_3$) 16.0 (*J* 7 Hz), 30.0, 31.0, 65.2 (*J* 6 Hz), 113.9, 122.1, 124.4, 126.0, 128.17, 128.69, 130.8, 116.8 (*J* 2 Hz), 122.4 (*J* 5 Hz), 138.7, 139.3 (*J* 2 Hz), 151.5 (*J* 8 Hz), 162.8 (*J* 1 Hz); δ_P (202.5 MHz, $CDCl_3$) −6.13 (pent, *J* 8.3 Hz); *m/z* (FAB) 402.1 (100%, MH^+).

4.13.13. Reaction of quinoline-2,4-dione 2a with triethyl phosphite: diethyl (5-benzyl-3a-butyl-2,4-dioxo-2,3a,4,5-tetrahydrofuro[2,3-*c*]quinolin-1-yl)phosphonate (19). A mixture of **2a** (120 mg, 0.27 mmol) and triethyl phosphite (1.91 g, 11.56 mmol) in toluene (5 mL) was heated to reflux for 14 h. After removal of the solvents, the residue was purified by chromatography on neutral aluminum oxide (20% EtOAc/benzene) to give **19** (68 mg, 52%) as a yellow amorphous solid. Found: C, 64.49; H, 6.43; N, 2.87. $C_{26}H_{30}O_6NP$ requires: C, 64.59; H, 6.25; N, 2.90%. R_f (20% EtOAc/toluene) 0.34; ν_{max} ($CHCl_3$) 3014, 2964, 2934, 1769, 1703, 1619, 1602, 1251, 1028, 980 cm^{-1}; δ_H (300.1 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.1 Hz), 1.21, 1.40 (6H, 2×t, *J* 7.1 Hz), 1.22–1.37 (4H, m), 1.77, 2.2 (2H, 2×m), 4.01, 4.34 (4H, 2×m), 4.81, 5.51 (2H, 2×d, *J* 16.5, 15.9 Hz), 7.03 (1H, d, *J* 8.2 Hz), 7.18–7.36 (6H, m), 7.44 (1H, dt, *J* 8.2, 1.1 Hz), 8.28 (1H, dd, *J* 7.7, 1.7 Hz); δ_C (75.5 MHz, $CDCl_3$) 13.6, 16.8 (*J* 6 Hz), 17.0 (*J* 6 Hz), 22.2, 24.7, 37.6, 47.0, 63.2 (*J* 6 Hz), 63.8 (*J* 6 Hz), 87.3 (*J* 16 Hz), 113.3, 116.2, 117.0, 123.9, 126.3, 127.7, 129.0, 131.3, 134.2, 135.7, 139.1, 166.4, 167.0; δ_P (202.5 MHz, $CDCl_3$) 5.48 (pent, *J* 18.9 Hz); *m/z* (EI) 483 (1, M^+), 399 (17), 353 (12), 336 (2), 298 (2), 263 (3), 206 (3), 143 (3), 91 (100), 65 (8), 57 (8%).

Acknowledgements

The research has been supported by the Ministry of Education of the Czech Republic (projects Nos. MSM223100001, MSM265200015, and MSM7088352101) and Czech Science Foundation (Grant No. 203/07/0320). Elemental analyses and measurements of some NMR spectra were carried out in the Central Laboratories of the Prague Institute of Chemical Technology. The authors thank to Prof. Dr. Miroslav Strnad (Palacký University & Institute of Experimental Botany AS CR, Olomouc, Czech Republic) for a biochemical assay of synthezised quinoline-2-ones.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.07.058.

References and notes

1. (a) Neuenhaus, W.; Budzikiewicz, H.; Korth, H.; Pulverer, G. *Z. Naturforsch.* **1979**, *34b*, 313–315; (b) Kitamura, S.; Nashizume, K.; Iida, T.; Miyashita, E.; Shirahata, K.; Kase, H. *J. Antibiot.* **1986**, *39*, 1160–1171; (c) Laschober, R.; Stadlbauer, W. *Liebigs Ann. Chem.* **1990**, 1083–1086.
2. (a) Faber, K.; Stückler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1177–1181; (b) Faber, K.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1881–1883; (c) Faber, K.; Steininger, H.; Kappe, T. *J. Heterocycl. Chem.* **1985**, *22*, 1081–1085; (d) Klásek, A.; Kořistek, K.; Kafka, S.; Košmrlj, J. *Heterocycles* **2003**, *60*, 1811–1820.
3. Closse, A.; Haefliger, W.; Hauser, D. *J. Med. Chem.* **1981**, *24*, 1465–1771.
4. (a) Kafka, S.; Klásek, A.; Kovář, M.; Kappe, T. *J. Heterocycl. Chem.* **1996**, *33*, 1977–1982; (b) Klásek, A.; Kafka, S. *J. Heterocycl. Chem.* **1998**, *33*, 307–311.
5. (a) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 1996; Vol. 639; (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123 (Tetrah.

Rep. No. 221); (c) *Organo-fluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993.
6. (a) Ge, P.; Kirk, K. *J. Fluorine Chem.* **1997**, *84*, 45–47; (b) Ge, P.; Kirk, K. *J. Org. Chem.* **1997**, *62*, 3340–3343; (c) Komatsu, Y.; Kitazume, T. *J. Fluorine Chem.* **1998**, *87*, 101–104.
7. (a) Patrick, T. B.; Lanahan, M. V.; Yang, C.; Walker, J. K.; Hutchinson, C. L.; Neal, B. E. *J. Org. Chem.* **1994**, *59*, 1210–1212; (b) Kvíčala, J.; Vlasáková, R.; Plocar, J.; Paleta, O.; Pelter, A. *Collect. Czech. Chem. Commun.* **2000**, *65*, 773–778.
8. Paleta, O.; Pomeisl, K.; Kafka, S.; Klásek, A.; Kubelka, V. *Beilstein J. Org. Chem.* **2005**, *1*, 1–17.
9. *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; The Synthesis and Reactions of Organic Compounds; Pergamon: Oxford, 1979; Vol. 2, pp 1316–1325.
10. (a) Litchtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607–616; (b) Spencer, E. Y.; Todd, A. R.; Webb, R. F. *J. Chem. Soc.* **1958**, 2968–2972; (c) Müller-Bötticher, H.; Fessner, W.-D.; Melder, J. P.; Prinzbach, H.; Gries, S.; Irngartinger, H. *Chem. Ber.* **1993**, *126*, 2275–2298; (d) Boulos, L. S.; Yakout, E. M.; Sidky, M. M. *Phosphorus Sulfur* **1984**, *21*, 47–52; (e) Wiley, D. W.; Simmons, H. E. *J. Org. Chem.* **1964**, *29*, 1876–1879.
11. Thiem, J.; Rash, D.; Paulsen, H. *Chem. Ber.* **1976**, *109*, 3588–3597.
12. (a) Kitazume, T. *Synthesis* **1986**, 855–856; (b) Morikawa, T.; Uchida, J.; Hasegawa, Y.; Taguchi, T. *Chem. Pharm. Bull.* **1991**, *39*, 2462–2464.
13. (a) Borowitz, I. R.; Firstenberg, S.; Borowitz, G. B.; Schuessler, D. *J. Am. Chem. Soc.* **1972**, *94*, 1623–1628; (b) Borowitz, I. R.; Firstenberg, S.; Casper, E. W. R.; Crouch, R. K. *J. Org. Chem.* **1971**, *36*, 3282–3289.
14. Exner, O. *Correlation Equations in Organic Chemistry (Czech)*; SNTL/ALFA: Praha, 1981; Chapter 6.
15. (a) Patai, S.; Schwartz, A. *J. Org. Chem.* **1960**, *25*, 1232–1234; (b) McIntosh, J. M.; Sieler, R. A. *Can. J. Chem.* **1978**, *56*, 226–231; (c) Janecki, T.; Kuś, A.; Krawczyk, H.; Błaszczyk, E. *Synlett* **2000**, 611–614.
16. Monaco, E. A., III; Beaman-Hall, C. M.; Mathur, A.; Lou Vallano, M. *Biochem. Pharmacol.* **2004**, *67*, 1947–1964.
17. Englund, B. *Org. Synth.* **1963**, *Coll. Vol. IV*, 184–186.
18. Englund, B. *Org. Synth.* **1963**, *Coll. Vol. IV*, 423–424.
19. Chengxin, Z.; Quing-Yun, Ch. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1741–1747.
20. Kvíčala, J.; Paleta, O.; Dědek, V. *J. Fluorine Chem.* **1990**, *47*, 441–457.
21. Paleta, O.; Pošta, A. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1427–1437.
22. Barth, F.; O-Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121–1124.