Bis(acetylaryl) podands in the synthesis of fluorine-containing bis(β-diketones) joined by a polyether spacer

*D. L. Chizhov, P. A. Slepukhin, I. G. Ovchinnikova, O. V. Fedorova, G. L. Rusinov,
V. I. Filyakova,⋆ and V. N. Charushin*

*I. Ya. Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences,
22/20 ul. S. Kovalevskoi, 620041 Ekaterinburg, Russian Federation.
Fax: +7 (343) 369 3058. E-mail: vif@ios.uran.ru*

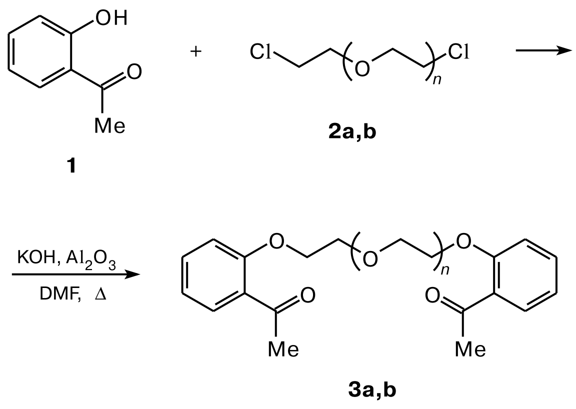
O-Alkylation of 2-acetylphenols with α,ω-dichloro derivatives of oligoethylene glycols in the presence of KOH and Al_2O_3 in DMF gave the corresponding podands. Their condensation with ethyl trifluoroacetate afforded fluorine-containing bis(β-diketones) with the aryl fragments linked by conformationally flexible polyether spacers.

Key words: the Williamson reaction, O-alkylation, phenols, podands, ethyl trifluoroacetate, organofluorine compounds, β-diketones, nanosized alumina, X-ray diffraction analysis.

The ability of acyclic polyethers (podands) to form lipophilic molecular complexes with metal ions and organic molecules are widely used in organic and analytical chemistry (phase-transfer catalysis, complexing agents, and extracting agents); the tendency of podands toward intra- and intermolecular noncovalent bonding is of interest for supramolecular chemistry.[1—3] Podands can be modified, *e.g.*, by attaching various polyfunctional and heterocyclic fragments to the ends of the polyoxyethylene chain. In particular, very promising is the synthesis of podands containing terminal 1,3-dicarbonyl fragments that can not only chelate most metal ions but also undergo various transformations and heterocyclizations. The synthetic potential of 1,3-dicarbonyl fragments provides prerequisites for the design of new podands. Podands and macrocycles with 1,3-dicarbonyl fragments have been reported;[4] however, the literature data on their fluorine-containing analogs are lacking. At the same time, it is known that a combination of electronic and steric factors makes fluorine-containing compounds substantially different in reactivity from nonfluorinated analogs. In addition, fluorinated organic molecules are more volatile and more lipophilic and penetrate better across cell membranes, which enhances their biological activity or changes the spectrum of their action. In some cases, fluorine atoms are involved in specific intermolecular interactions.[5] Earlier,[6] we have reported on the synthesis of bis(aryl) podands modified with the fragments of fluoroalkyl-containing 1,3-enamino ketones.

In the present work, we developed a preparative synthesis of bis(acetylaryl) podands and the corresponding fluorine-containing bis(β-diketones) with conformationally flexible polyether spacers linking the aryl fragments (Schemes 1 and 2).

Scheme 1



2, 3: *n* = 1 (**a**), 2 (**b**)

Bis(acetylaryl) podands **3a,b** were obtained by the Williamson reactions of 2-hydroxyacetophenone (**1**) with α,ω-dichloro derivatives of di- and triethylene glycols **2a,b**.

As applied to compound **1**, the Williamson reaction is usually accompanied by side processes (in particular, its self-condensation), which considerably lowers the yield of the target product. For instance, bis(acetylaryl) podand **3a** has been obtained earlier[7] in 30% yield by heating compounds **1** and **2a** with NaOH in a molar ratio of 2 : 1 : 2 (DMF, 95 °C, 100 h). We found that in the presence of KOH at 100 °C, the yields of products **3a** and **3b** are 21 and 18%, respectively, even in 12 h. At longer reaction times, the yields increase only slightly. Addition of basic Al_2O_3 (10 mol.%) doubles the yields of compounds **3a,b**; in the presence of the same amount of nanosized Al_2O_3 (20—50 nm), their yields increase by a factor of 2.7—3

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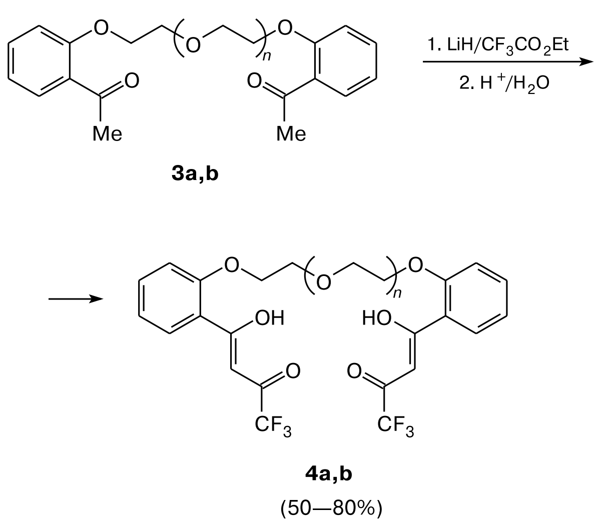
Scheme 2



3a,b

4a,b (50—80%)

n = 1 (**a**), 2 (**b**)

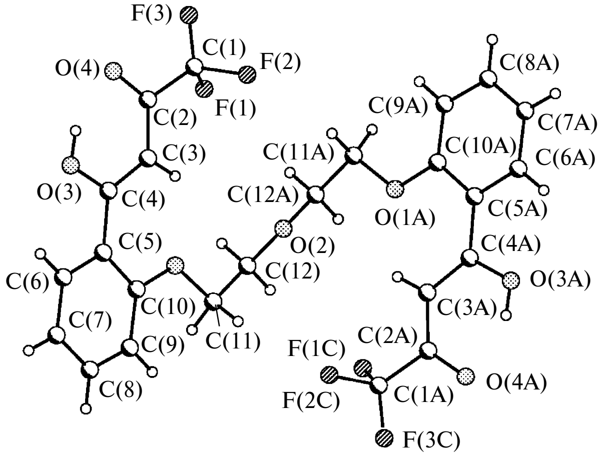


Fig. 1. General view of structure **4a** with the atomic numbering adopted in crystallographic experiments (the symmetry-equivalent atoms are indicated with letters).

(see Scheme 1, Table 1). The above effects can be explained by chelating adsorption of 2-hydroxyacetophenone **1** and/or its potassium salt at Al_2O_3. This deactivates the carbonyl group, thus preventing compound **1** from competitive self-condensation but not from the Williamson reaction.

Condensation of bis(acetylaryl) podands **3a,b** with ethyl trifluoroacetate in the presence of LiH gave fluorine-containing bis(β-diketones) **4a,b** in 50—80% yields. In the products obtained, the 1,3-dicarbonyl fragments are linked by conformationally flexible polyether spacers (see Scheme 2).

The molecular formulas and structures of bis(β-diketones) **4a,b** were proved by elemental analysis, IR spectroscopy, and ^{1}H and ^{19}F NMR spectroscopy. According to ^{1}H NMR spectra in $CDCl_3$, compounds **4a,b** are symmetrical and completely enolized. The spectra show one set of signals, in particular, broadened singlets at δ ~15.2 (OH) and singlets at δ 7.15—7.17 (=CH). The ^{19}F NMR spectra of compounds **4a,b** contain a singlet at δ 85.38 (CF_3).

Structure **4a** was confirmed by X-ray diffraction analysis. The molecule is in the special position on axis C_2 (Fig. 1) and has an S-shaped configuration with approaching terminal (aryl) groups, which is characteristic of the earlier described chalcone podands.[8] The torsion angle of the polyether fragment O(1)—C(11)—C(12)—O(2) is 66.51°. The angle between the planes of the aryl rings is 78.85°. The keto enol fragments are oriented in opposite directions from the central axis C_2 of the molecule, being involved in no additional intra- or intermolecular short contacts (see Fig. 1). Either keto enol fragment is coplanar with the aromatic ring (the largest deviation of the atoms from the mean-square plane is 0.12 Å for the terminal C(1) atom). The bond lengths and bond angles in this fragment are close to standard values (Table 2). The lengthening of the C(4)—O(3) and C(2)—C(3) bonds compared to the O(4)—C(2) and C(3)—C(4) bonds (see Table 2) indicates the enolized carbonyl group at the aromatic substituent. The keto enol fragments are in the U-conformation stabilized by the intramolecular hydrogen bond O(3)—H(3B)...O(4) (O(3)—H(3B), 0.820 Å; H(3B)...O(4), 1.767 Å; the angle O(3)H(3B)O(4), 150.22°; O(3)...O(4), 2.512(3) Å). The F atoms of the trifluoromethyl group are disordered in three positions with populations of 0.4, 0.4, and 0.2. Because of the overlap of their thermal ellipsoids, the F atoms were refined in a partial isotropic approxima-

Table 1. Effect of Al_2O_3 on the yields of products **3a,b**

Product	Yield* (%)		
	Without Al_2O_3	Basic Al_2O_3	Nanosized Al_2O_3
3a	21	42	57
3b	18	39	54

* The reaction time is 12 h.

Table 2. Selected bond lengths d and bond angles ω in structure **4a**

Bond	d/Å	Angle*	ω/deg
C(4)—O(3)	1.299(3)	C(12)$^{\#1}$—O(2)—C(12)	110.6(3)
O(4)—C(2)	1.230(3)	C(10)—O(1)—C(11)	118.86(18)
C(3)—C(2)	1.381(3)	C(4)—C(3)—C(2)	120.8(2)
C(3)—C(4)	1.375(3)	O(3)—C(4)—C(3)	118.9(2)
C(4)—C(5)	1.456(3)	O(4)—C(2)—C(3)	125.6(3)
C(2)—C(1)	1.503(4)		

* The symmetry operation code is $^{\#1}$ $-x, y, -z$.

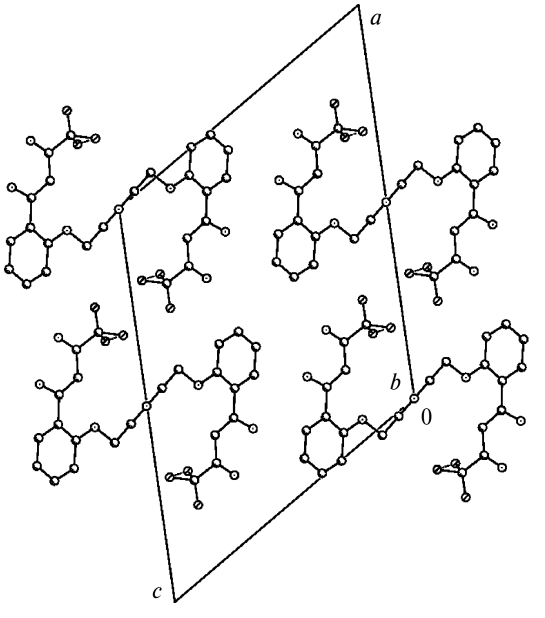


Fig. 2. Molecular packing of compound **4a** along the axis *b*.

tion (insertion of the instruction ISOR 0.01 into the ins.file of the SHELXL software).

The molecular packing of compound **4a** consists of its molecules stacked along the axis *b* (Fig. 2), the spatial orientation of the molecules being identical in all stacks (Fig. 3).

It should be noted that the Cambridge Crystallographic Data Collection contains only three 1,3-diketone structures with trifluoromethyl and aryl substituents at the dicarbonyl pentad. In those structures,[9—11] the carbonyl group at the aromatic substituent is enolized, which is well consistent with our X-ray diffraction data for compound **4a**.

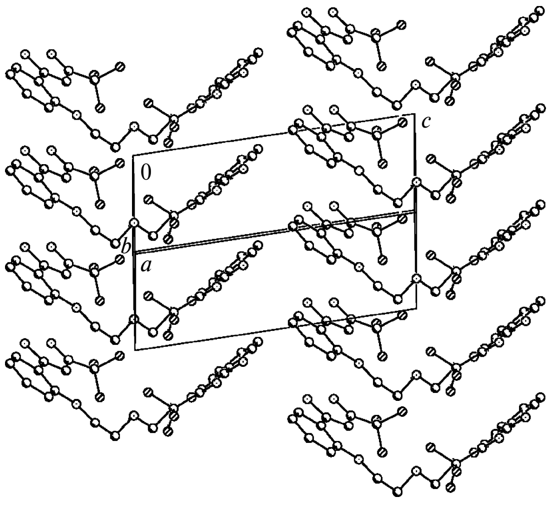


Fig. 3. Molecular packing of compound **4a** running parallel to the plane *ab*.

Thus, we developed simple and convenient methods for the synthesis of bis(acetylaryl) podands **3** and fluorine-containing bis(β-diketones) **4** with polyether spacers. These methods have undoubted advantages over the known four-step route to similar nonfluorinated structures.[4] By using reactions familiar with fluorine-containing 1,3-diketones and bis(β-diketones), the dicarbonyl (keto enol) fragments of compounds **4** can be transformed into other functional groups or involved in heterocyclizations retaining the polyether fragment to obtain bis(1-aminopropen-3-ones), bis(pyrazoles), bis(isoxazoles), bis(pyrimidines), bis(benzodiazepines), *etc.*[12]

Experimental

The course of the reactions was monitored by TLC on Silufol UV-254 plates with $CHCl_3$ as an eluent. Spots were visualized in aqueous solutions of copper acetate and $KMnO_4$. ^1H and ^{19}F NMR spectra were recorded on a Bruker DRX-400 spectrometer (400 (^1H) and 376 MHz (^{19}F)) with $SiMe_4$ and C_6F_6 as the internal standards, respectively. IR spectra were recorded on a Spectrum One B FTIR spectrometer (Perkin—Elmer).

X-ray diffraction analysis was carried out for a colorless crystal stub (0.43×0.36×0.28 mm) on an Xcalibur 3 automatic four-circle diffractometer with a CCD detector according to a standard procedure (Mo-Kα radiation, graphite monochromator, ω scan mode, scan step 1°, $T = 295(2)$ K). No absorption correction was applied. The crystal is monoclinic, space group *C*2; the unit cell parameters: $a = 19.438(6)$ Å, $b = 4.5630(9)$ Å, $c = 15.404(6)$ Å, $\beta = 122.297(12)°$, $V = 1154.8(6)$ Å^3, $Z = 2$ for the molecular formula $C_{24}H_{20}F_6O_7$; $d_{calc} = 1.537$ g cm^{-3}, $\mu = 0.143$ mm^{-1}, $F(000) = 548$, θ scan range 2.77—26.44°. The number of measured reflections is 3461; the number of independent reflections is 1315 ($R_{int} = 0.0180$), including 719 reflections with $I > 2\sigma(I)$. The scan completeness for $\theta = 26.44°$ is 97.3%. The structure was determined and refined with the SHELX program package.[13] The structure was solved by the direct method and refined by the full-matrix least-squares method on F^2. All non-hydrogen atoms were refined anisotropically; the hydrogen atoms were located geometrically and refined using a riding model with dependent thermal parameters. Final residuals are $R_1 = 0.0286$ and $wR_2 = 0.0545$ for the reflections with $I > 2\sigma(I)$) and $R_1 = 0.0620$ and $wR_2 = 0.0574$ for all reflections ($S = 1.007$). The maximum and minimum residual electron densities are 0.084 and −0.077 e Å^{-3}, respectively.

The X-ray diffraction data obtained have been deposited with the Cambridge Crystallographic Data Center (No. 796 588) and are available from www.ccdc.cam.ac.uk/data_request/cif.

Acetylaryl podands 3a,b. 2-Hydroxyacetophenone (0.14 mol), KOH (0.14 mol), and 10 mol.% basic alumina (Chemapol 5/40) or nanosized alumina (0.007 mol) prepared by the gas-phase method[14] were added to a solution of α,ω-dichloro derivative **2** (0.07 mol) in DMF (100 mL). The reaction mixture was stirred at 100 °C for 12 h and filtered. The filtrate was diluted with water (700 mL). The resulting precipitate was filtered off and purified by flash chromatography (SiO_2, chloroform). The eluate was concentrated; the product was washed on a filter with a small amount of methanol and dried in air. The yields of compounds **3a,b** are given in Table 1.

1,5-Bis(2-acetylphenoxy)-3-oxapentane (3a), colorless needles. The yield was 57%, m.p. 76—77 °C. Found (%): C, 70.23; H, 6.53. $C_{20}H_{22}O_5$. Calculated (%): C, 70.17; H, 6.43. ^{1}H NMR (DMSO-d$_6$), δ: 2.50 (s, 6 H, Me); 3.88—3.90, 4.24—4.26 (both m, 8 H, O—CH$_2$—CH$_2$); 7.01 (dd, 2 H, Ar, *J* = 8.3 Hz, *J* = 7.7 Hz); 7.16 (d, 2 H, Ar, *J* = 7.7 Hz); 7.51 (ddd, 2 H, Ar, *J* = 8.3 Hz, *J* = 7.7 Hz, *J* = 1.8 Hz); 7.57 (dd, 2 H, Ar, *J* = 7.7 Hz, *J* = 1.8 Hz). IR (Nujol, paste), ν/cm^{-1}: 1660 (C=O); 1257, 1145, 1060, 1040 (C—O—C).

1,8-Bis(2-acetylphenoxy)-3,6-dioxaoctane (3b), colorless needles. The yield was 54%, m.p. 73—74 °C. Found (%): C, 68.42; H, 6.68. $C_{22}H_{26}O_6$. Calculated (%): C, 68.39; H, 6.73. ^{1}H NMR (DMSO-d$_6$), δ: 2.54 (s, 6 H, Me); 3.62 (s, 4 H, O—CH$_2$); 3.79—4.82, 4.19—4.21 (both m, 8 H, O—CH$_2$—CH$_2$); 7.00 (ddd, 2 H, Ar, *J* = 8.3 Hz, *J* = 7.7 Hz, *J* = 0.8 Hz); 7.14 (dd, 2 H, Ar, *J* = 8.4 Hz, *J* = 0.8 Hz); 7.50 (ddd, 2 H, Ar, *J* = 8.4 Hz, *J* = 7.6 Hz, *J* = 2.0 Hz); 7.56 (dd, 2 H, Ar, *J* = 7.6 Hz, *J* = 2.0 Hz). IR (Nujol, paste), ν/cm^{-1}: 1661 (C=O); 1255, 1145, 1062, 1040 (C—O—C).

1,5-Bis[2-(4,4,4-trifluoro-1-hydroxy-3-oxobut-1-enyl)phenoxy]-3-oxapentane (4a). Two drops of MeOH were added to a mixture of LiH (0.25 g, 31.3 mmol), bis(acetyl) podand **3a** (1.71 g, 5.0 mmol), and ethyl trifluoroacetate (5.00 g, 35.0 mmol) in hexane (50 mL) and dry THF (20 mL). The reaction mixture was stirred at ~20 °C for 40 min and then refluxed with stirring for 6 h, while monitoring its composition by TLC. The solvents were removed to dryness. The residue was washed with hexane, dried in air, and carefully placed in 10% HCl (100 mL). The resulting suspension was stirred for 3 h. The precipitate was filtered off, washed with water, dried, and recrystallized from toluene. The yield was 1.31 g (49%), yellowish crystals, m.p. 151—152 °C. Found (%): C, 53.67; H, 4.01; F, 21.18. $C_{24}H_{20}F_6O_7$. Calculated (%): C, 53.94; H, 3.77; F, 21.33. ^{1}H NMR (CDCl$_3$), δ: 3.96—3.98 (m, 4 H, 2 CH$_2$); 4.26—4.28 (m, 4 H, 2 CH$_2$); 6.97 (dd, 2 H, Ar, *J* = 8.5 Hz, *J* = 0.6 Hz); 7.08 (td, 2 H, Ar, *J* = 7.9 Hz, *J* = 0.6 Hz); 7.17 (s, 2 H, —CH=); 7.52 (ddd, 2 H, Ar, *J* = 8.5 Hz, *J* = 7.3 Hz, *J* = 1.8 Hz); 8.00 (dd, Ar, *J* = 7.9 Hz, *J* = 1.8 Hz); 15.21 (br.s, 2 H, OH). ^{19}F NMR (CDCl$_3$), δ: 85.38 (s). IR (Nujol, suspension), ν/cm^{-1}: 3151 (=CH); 1599, 1588 (C=O—C=C).

1,8-Bis[2-(4,4,4-trifluoro-1-hydroxy-3-oxobut-1-enyl)phenoxy]-3,6-dioxaoctane (4b). One drop of MeOH was added to a mixture of LiH (0.05 g, 6.3 mmol), bis(acetyl) podand **3b** (0.386 g, 1.0 mmol), and ethyl trifluoroacetate (1.00 g, 7.0 mmol) in hexane (20 mL). The reaction mixture was stirred at ~20 °C for 30 min and then refluxed with stirring for 1 h. On cooling to ~20 °C, ether (20 mL) was added and the reaction mixture was refluxed with stirring for 5 h, while monitoring its composition by TLC. The ether was removed and the precipitate that formed was filtered off and carefully placed in 10% HCl (50 mL). The resulting oil was stirred to crystallization and the crystals were filtered off, washed with water, dried in air, and recrystallized from heptane. The yield was 0.45 g (78%), cream-colored crystals, m.p. 110—111 °C. Found (%): C, 54.11; H, 4.27; F, 19.65. $C_{26}H_{24}F_6O_8$. Calculated (%): C, 53.98; H, 4.18; F, 19.71. ^{1}H NMR (CDCl$_3$), δ: 3.73 (s, 4 H, (OCH$_2$)$_2$); 3.90 (m, 4 H, 2 C$\underline{H}_2$OCH$_2$); 4.23 (m, 4 H, 2 ArOCH$_2$); 6.95 (d, 2 H, Ar, *J* = 8.4 Hz); 7.06 (t, 2 H, Ar, *J* = 7.6 Hz); 7.16 (s, 2 H, =CH); 7.50 (m, 2 H, Ar); 7.99 (dd, 2 H, Ar, *J* = 7.6 Hz, *J* = 1.3 Hz); 15.18 (br.s, 2 H, 2 OH). ^{19}F NMR (CDCl$_3$), δ: 85.38 (s). IR (Nujol, suspension), ν/cm^{-1}: 3159 (=CH); 1600, 1567 (C=O—C=C).

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