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CHEMISTRY

Synthesis and Structure of (1S)-{2-[(1*S*)-Hydroxyethyl]phenyl}-1-phenyl-2,2,2-trifluoroethanol

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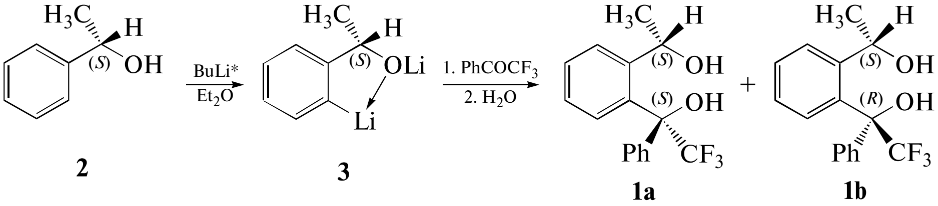
In recent years, there has been growing interest in organofluorine compounds due to their anomalous physical properties and high biological activity. This is exemplified by recently developed antiallergic pharmaceutical Fluticasone [1]. Optically active fluorine-containing alcohols and ketones are important building blocks in organic synthesis.

In this paper, we describe the synthesis of (1*S*)-{2-[(1*S*)-hydroxyethyl]phenyl}-1-phenyl-2,2,2-trifluoroethanol (**1a**) based on (*S*)-1-phenylethanol (**2**) (Scheme 1). We have shown previously [2] that the condensation of *ortho*-lithiated alcohol (**3**) with benzophenones allows preparation of chiral 1,4-diols useful as chiral catalysts similarly to BINOLs [3] and TADDOLs [4].



*1.1 equiv. of *n*-BuLi, then 1.1 equiv. of *sec*-BuLi.

Scheme 1.

Initially, lithiation procedures were tested using racemic alcohol **4**. The lithiation of **4** by reacting with 2 equivalents of *n*-BuLi followed by condensation with PhCOCF$_3$ leads to desired diol **7** in a yield not higher 29% (Scheme 2). The NMR spectrum of the reaction mixture indicates the presence of byproducts, mainly compounds **8** and **10**. Their formation can be explained by the reduction of trifluoroacetophenone with lithium alcoholate **5** followed by reaction of enol **9** (resulting from the oxidation of compound **5**) with PhCOCF$_3$. Such a reduction with lithium alcoholates was observed in the work [5] for perfluoroalkyl phenyl ketones. It should be noted that we did not observe the formation of compounds of type **8** and **10** in the condensations with other ketones containing no fluorine, this fact seems to be caused by the much higher reactivity of PhCOCF$_3$.

The low yields of the diol and considerable amounts of byproducts are likely to result from the insufficient basicity of *n*-BuLi to provide *ortho*-lithiation. The replacement of the second equivalent of *n*-BuLi by *sec*-BuLi led to a considerable increase in the yield of **7** (65%).

The reaction proceeds nonselectively to form two diastereomeric diols (**7a** and **7b**) in 1.3 : 1 ratio. The major diastereomer **7a** was isolated from reaction mixture by crystallization from a petroleum ether–diethyl ether mixture. We failed to obtain second diastereomer **7b** in a pure state.

The synthesis of chiral diastereomeric diols **1a** and **1b** from compound **2** was carried out by procedure developed for the racemic alcohol (Scheme 1).

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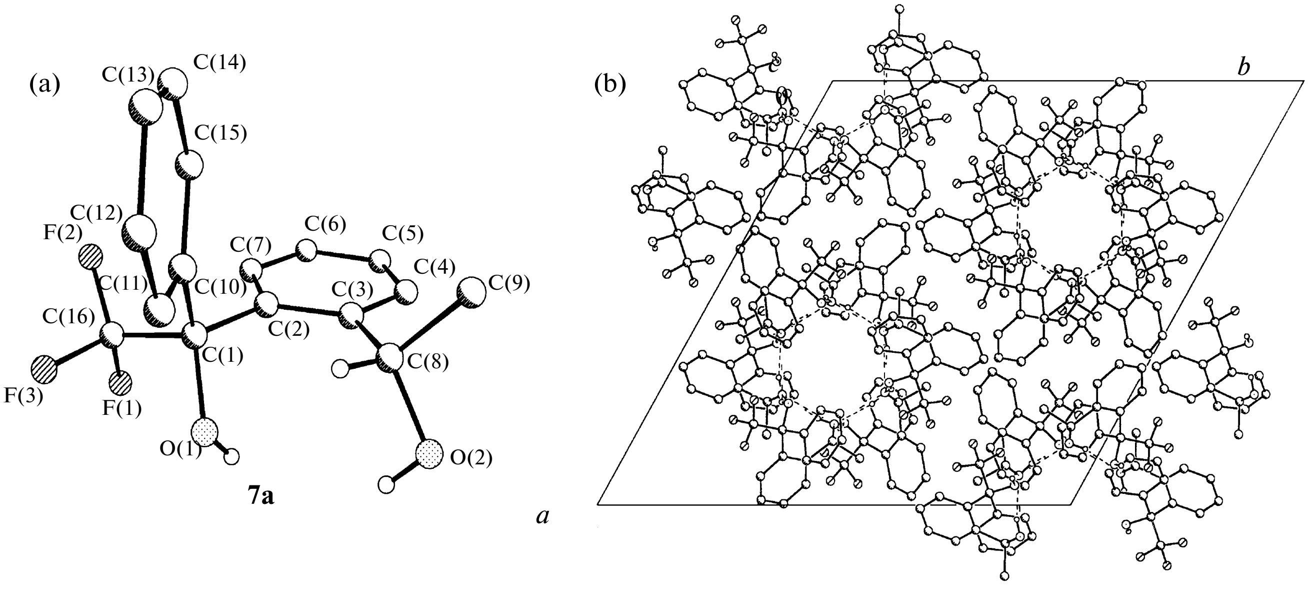
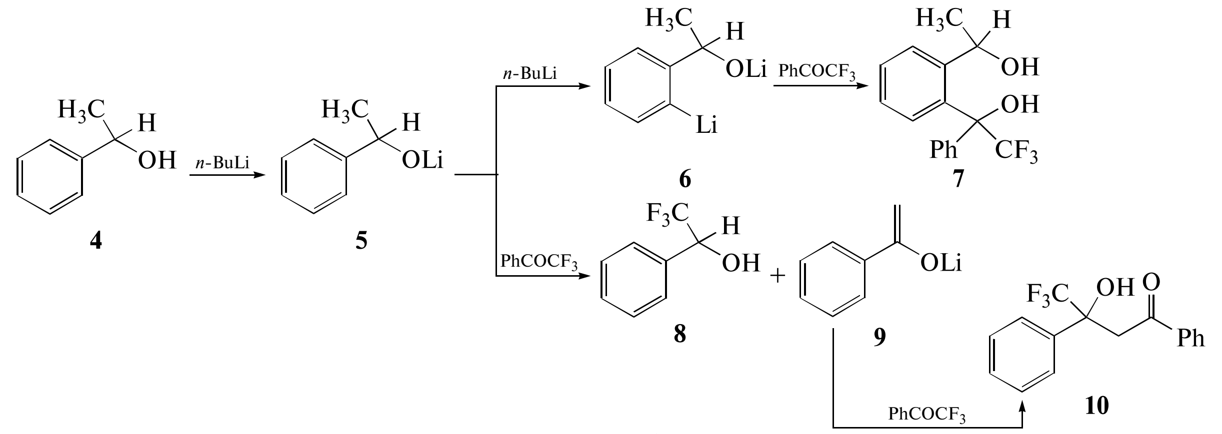


Fig. 1. (a) Structure of diol **7a** (some hydrogen atoms are omitted for clarity); (b) a fragment of crystal packing along the *c* crystallographic axis.

We isolated chiral diol **1a** in pure state but failed to grow a crystal suitable for X-ray diffraction study. Therefore, we performed X-ray diffraction analysis for racemic diol **7a** and found that the configuration of the nascent chiral center is the same as that of the initial alcohol (Fig. 1a). Thus, we may attribute (*S,S*) configuration to the major diastereomer **1a** prepared from compound **2**.



Scheme 2.

According to X-ray diffraction study, the geometrical parameters of diol **7a** is within the range typical for this class of compounds. It is interesting to note that **7a** molecules in crystal unite to form hexamers produced due to hydrogen bonds of average strength (O···O 2.7386(7)–2.8212(12) Å, ∠OHO 153(1)–172(1)°) and composed of alternating molecules of different chirality, (*S,S*) and (*R, R*), around the *c* crystallographic axis (Figs. 1 and 2). The six-membered pseudo-ring composed of oxygen atoms involved into hydrogen bonding has a shape intermediate between chair and half-boat conformations and has the following puckering parameters: the total puckering amplitude $S = 0.410$, the polar angle $\theta = 16.0°$, and the phase angle $\psi_2 = 0°$ [6].

To describe quantitatively hydrogen bonding, we performed a topological analysis of total electron density distribution function obtained through precise X-ray diffraction study of crystal of compound **7a** in the context of the Bader theory [7]. Interaction energy was estimated on the basis of the Espinosa–Lecomte semiquantitative correlation [8, 9] developed and suc-

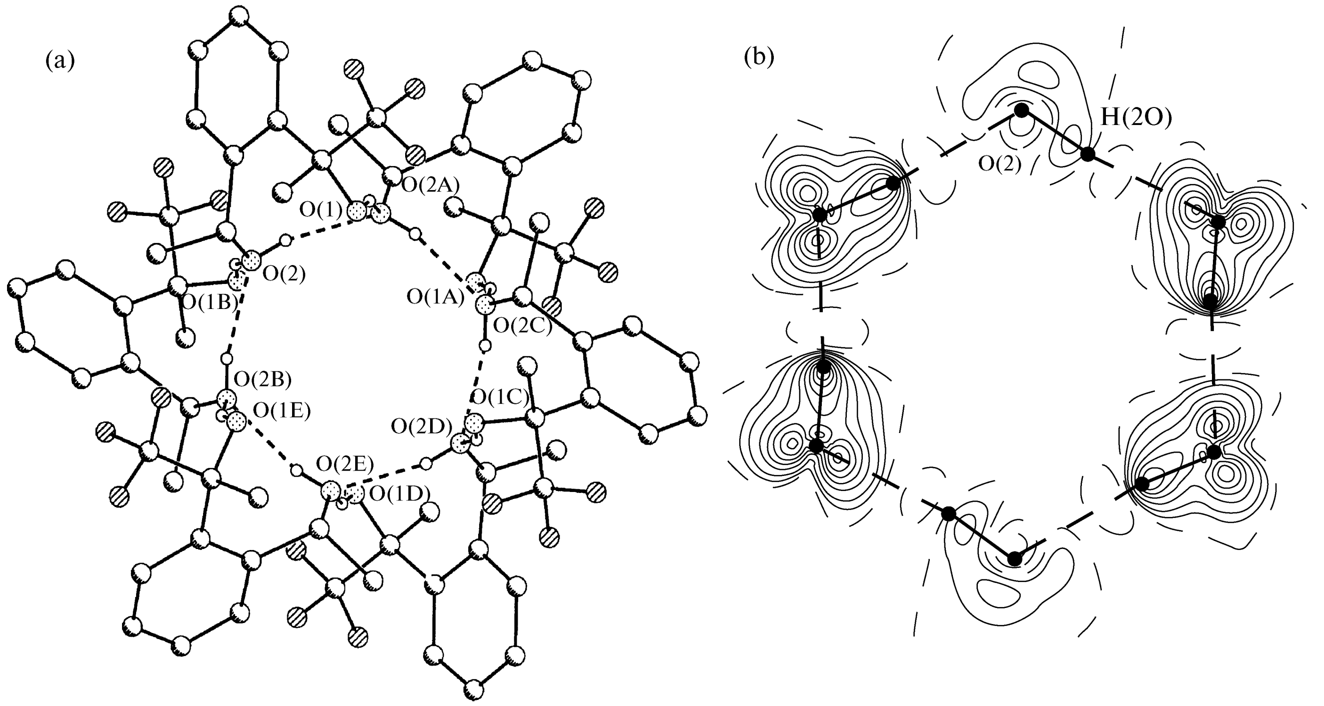


Fig. 2. Hydrogen-bonded hexamer formed by six molecules of diol **7a** in crystal. (a) A structure of hexamer; (b) distribution of deformation electron density in the region of six-membered ring formed by O(2)–H(2O)···O(2) hydrogen bonds (the ring has chair conformation, two of six oxygen atoms are displaced from figure plane). Contour lines are plotted with step of 0.1 eÅ^{-3}, nonpositive contours are shown by dashed lines.

cessfully used to describe hydrogen bonding [10, 11]. The resulting energies of the O(1)–H(1O)···O(2) and O(2)–H(2O)···O(2) hydrogen bonds in the crystal of **7a** were found to be 5.2 and 7.4 kcal/mol, respectively. For comparison, the corresponding value for a hexamer built of water molecules in a crystal of piperidine-2-carboxylic acid tetrahydrate [11] is within 5.2–8.9 kcal/mol with a stabilization energy of 7.2 kcal/mol (per water molecule).

The stabilization energy of the hexamer in the crystal of **7a** (on account of the presence of additional C–H···π contacts with an energy of about 1 kcal/mol) is higher than 13 kcal/mol; i.e., this associate is rather stable. The resulting cavity in it (about 35 Å^3 in volume) can accommodate, for example, a water molecule and hold it due to a system of hydrogen bonds. Similarly, diol **7a** can behave as a host when it forms clathrates with small molecules of close size. The noted hydrogen-bonded clusters unite with each other via weaker interactions of C–H···F and C–H···π types (minimal C···F and C···C distances are 3.4421(7) and 3.5813(7) Å, respectively) to form a 3D scaffold.

The measurement of CD spectra of diol **1a** with (*S*,*S*) configuration in the range 300–200 nm (Fig. 3) showed the presence of two Cotton effects (CE): a weak positive effect in the range of 270–250 nm and a strong positive one at 230 nm caused by electronic transitions in the aromatic chromophores. The short-wavelength positive Cotton effect of compound **1a** is similar to that observed for (*S*,*S*)-1,4-aminoalcohols obtained from (*S*)-*N*,*N*-dimethyl-1-phenylethylamine. Thus, CD spectra can be used to determine the configuration of the carbinol center formed in the reaction of derivatives of diaryl- and triarylcarbinols with aminoethyl or hydroxyethyl substituents in one of benzene rings.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian XR-400 spectrometer (operating at 400 MHz) in $CDCl_3$ solutions using TMS as an internal reference. IR spectra in CCl_4 were obtained with an UR-20 spectrophotometer; $[\alpha]_D^{20}$ was measured with an EPO-1 polarimeter (VNIEKIPRODMASh, Moscow) in ethanol in 0.25- and 0.1-dm cuvettes. CD spectra were measured on a JASCO J-600 dichrograph (Japan).

1-[2-(1-Hydroxyethyl)phenyl]-1-phenyl-2,2,2-trifluoroethanol (a mixture of diastereomeric diols 7a and 7b). A hexane solution of *n*-BuLi (5.5 mL of 2.0 M solution, 0.011 mol) and a hexane solution of *sec*-BuLi (7.8 mL of 1.4 M solution, 0.011 mol) were added sequentially to a solution of 1.22 g (0.01 mol) of 1-phenylethanol (**4**) in anhydrous ether in an argon atmosphere, the mixture was kept for 3.5 h, and then 1.7 g (0.095 mol) of trifluoroacetophenone was added. After 24 h, the mixture was treated with water, and the organic layer was separated and dried over $MgSO_4$. The solvent was removed, and unreacted phenylethanol was distilled off in a vacuum to give a mixture of diastereomeric diols in 1.3 : 1 ratio in 65% yield (determined from ^{1}H NMR spectra of reaction mixtures).

1-[2-(1-Hydroxyethyl)phenyl]-1-phenyl-2,2,2-trifluoroethanol (7a) was isolated by crystallization of a mixture of the diastereomeric diols **7** from petroleum ether (bp 40–70°C)–diethyl ether mixture. Mp 170°C.

^{1}H NMR (δ, ppm): 0.93 (d, 3H, $C\underline{H}_3$–$C\underline{H}$), 2.38(s, 1H, $O\underline{H}$), 4.91 (q, 1H, CH_3–$C\underline{H}$), 5.14 (s, 1H, $O\underline{H}$), 7.29–7.46 (m, 6H, arom.), 7.43 (t, 1H, arom.), 7.54 (d, 1H, arom.), 7.72 (d, 1H, arom.).

IR (KBr pellet, ν, cm^{-1}): 3490–3200 (wide, ν_{OH}); (CCl_4 solution): 3590 (narrow, ν_{OH}), 3520–3150 (wide).

For $C_{16}H_{15}F_3O_2$ anal. calcd. (%): C, 64.86; H, 5.10.

Found (%): C, 65.04; H, 5.04.

1-(1*S*)-[2-(1-Hydroxyethyl)phenyl]-1-phenyl-2,2,2-trifluoroethanol (a mixture of diastereomeric diols 1a and 1b) was obtained from (*S*)-1-phenylethanol similarly to racemic diols **7**. Yield 67%, diastereomer ratio is 1.3 : 1.

(1*S*)-{2-[(1*S*)-Hydroxyethyl]phenyl}-1-phenyl-2,2,2-trifluoroethanol (1a). The compound was isolated by crystallization of a mixture of diastereomeric diols **1** from petroleum ether (bp 40–70°C)–diethyl ether mixture. Mp 117°C, $[\alpha]_D^{20}$ —100.0° (*c* 1, ethanol).

^{1}H NMR (δ, ppm): 0.93 (d, 3H, $C\underline{H}_3$–CH), 2.38 (s, 1H, $O\underline{H}$), 4.91 (q, 1H, CH_3–$C\underline{H}$), 5.14 (s, 1H, $O\underline{H}$), 7.29–7.46 (m, 6H, arom.), 7.43 (t, 1H, arom.), 7.54 (d, 1H, arom.), 7.72 (d, 1H, arom.).

IR (KBr pellet, ν, cm^{-1}): 3490–3200 (wide, ν_{OH}); (CCl_4 solution): 3590 (narrow, ν_{OH}), 3520–3150 (wide).

For $C_{16}H_{15}F_3O_2$ anal. calcd. (%): C, 64.86; H, 5.10.

Found (%): C, 65.01; H, 5.01.

X-ray diffraction study of compound 7a. Crystals are rhombohedral at 100 K: $a = 22.437(1)$, $c = 14.429(1)$ Å, $V = 6290.7(6)$ Å^3, $d_{\text{calcd.}} = 1.408$ g cm^{-1}, space group $R\bar{3}$, $Z = 18$. The intensities of 66 694 reflections were measured on a Smart APREX2 CCD automated diffractometer at 100 K (MoK_α radiation, graphite monochromator, the ω scan mode, $2\theta_{\max} = 90°$) and 11 498 unique reflections ($R(int) = 0.0825$) were used in further calculations. The structure was solved by direct methods and refined by full-matrix least-squares techniques in the anisotropic–isotropic approximation on F^2. Hydrogen atoms were located from a difference Fourier syntheses and refined isotropically. The final residuals were: $wR_2 = 0.1350$, GOF = 1.005 for all reflections ($R_1 = 0.0434$ calculated for 8064 reflections with $I > 2\sigma(I)$) using the SHELXTL PLUS software complex.

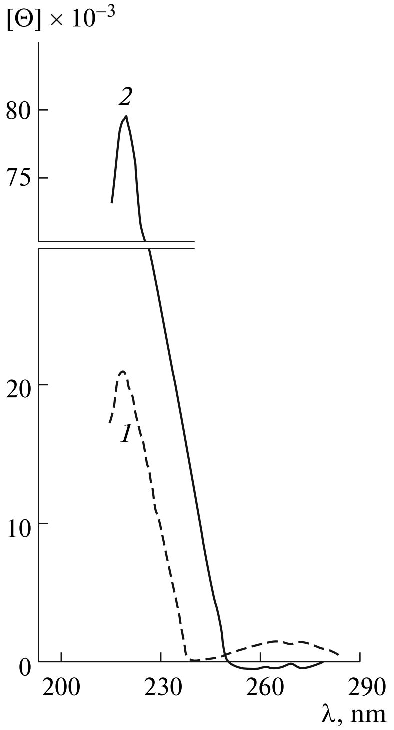


Fig. 3. CD spectra (in ethanol): *1*, (1*S*)-{2-[(1*S*)-hydroxyethyl]phenyl}-1-phenyl-2,2,2-trifluoroethanol, *2*, (1*S*)-1-{2-[(1*S*)-(dimethylamino)ethyl]phenyl}-1-phenyl-2,2,2-trifluoroethanol.

Multipole refinement of **7a** was carried out in the framework of the Hansen–Koppens formalism [12] using XD software package [13] with core and valence electron densities obtained from wave functions based on the relativistic solution of the Dirac–Fock equation. Prior to refinement, C–H and O–H bond distances were normalized to the standard values of 1.08 and 0.98 Å, respectively. Multipole expansion was confined by the octapole level for fluorine, oxygen, and carbon atoms and by the dipole level for hydrogen atoms. The refinement was performed for F_{hkl}. All covalently bonded atom pairs fulfill the Hirshfeld criterion for bond rigidity [14]. The residual electron density was not higher than 0.22 eÅ^{-3} (in proximity to the C(6) nucleus). The search for bonding interactions and calculation of topological characteristics of the electron density distribution function for them was carried out using the WINXPRO program [15]. The final residuals were: $R = 0.0330$, $Rw = 0.0364$, GOF = 0.8061 for 8056 reflections with $I > 3\sigma(I)$.

The full set of X-ray diffraction data was deposited with the Cambridge Crystallographic Data Centre (no. 772906) for compound **7a**, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam/ ac/uk).

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