Aromatization via a Dibromination–Double Dehydrobromination Sequence: A Facile and Convenient Synthetic Route to 2,6-Bis(trifluoroacetyl)phenols[1]

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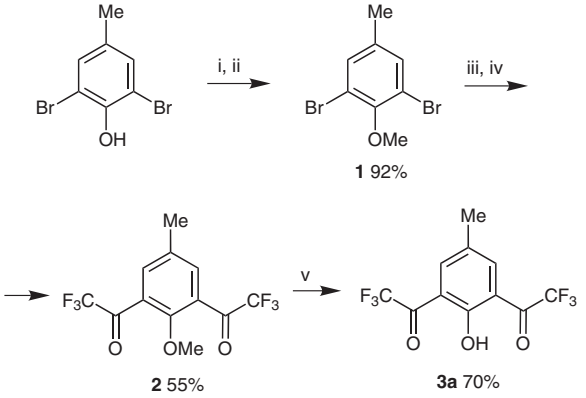
Abstract: An efficient and reliable method to synthesize 2,6-bis(trifluoroacetyl)phenols bearing various substituents in the 4-position was developed. These valuable fluorinated building blocks were obtained from the corresponding cyclohexanones in a facile and convenient procedure, demonstrated to be superior to the traditional approaches. The application of this methodology to cyclohexane-1,4-dione opened access to 2,5-bis(polyfluoroacyl)-1,4-hydroquinones. Structural peculiarities of the obtained phenols as well as their 1,3-dicarbonyl or 1,3,5-tricarbonyl precursors are discussed on the basis of multinuclear NMR spectroscopy.

Key words: fluorinated compounds, arenes, ketones, aromatization, phenols

The incorporation of polyfluoroalkyl moieties, especially the trifluoromethyl group, into organic molecules often results in remarkable changes in the physical properties, chemical reactivity, and biological activity of the derived compounds, thereby making them more attractive for diverse practical applications. In fact, fluorinated substances have already become indispensable in many fields of modern agrochemistry, pharmaceutical industry, and materials science.[3] Therefore, methods for the synthesis of fluorinated compounds that are simultaneously efficient, economically feasible, and suitable for scale-up remain a significant challenge for organic chemists.[4] For other work currently in progress in our laboratories, we required phenols bearing two fluoroacyl moieties in the aromatic ring. After extensive experimentation we succeeded in developing a facile, convenient, and reliable method to synthesize these previously unknown compounds. Our experimental findings and observations are summarized here.

The methodology to synthesize our first target compound, 4-methyl-2,6-bis(trifluoroacetyl)phenol (**3a**, Scheme 1), involved double acylation of *p*-cresol, promoted by a Lewis acid. 2,6-Diacetyl-4-methylphenol can be obtained easily in this way when an excess of acetyl chloride is used in the presence of aluminum trichloride.[5] Unfortunately, this method does not work for trifluoroacetyl chloride: instead, 2-trifluoroacetyl-4-methylphenol was the only product isolated.[6] To circumvent the problem, a multistep procedure in which 2,6-dibromo-4-methylphenol was used as the starting compound was employed (Scheme 1). In contrast to the related data of Ansong et al.,[7] double metalation and subsequent trifluoroacetylation produced **3a** (Scheme 1).



Scheme 1 Synthesis of phenol **3a** starting from 2,6-dibromo-4-methylphenol. *Reagents and conditions*: (i) aq NaOH (1.6 equiv); (ii) Me_2SO_4 (1 equiv), 40–100 °C, 30 min; (iii) BuLi (2 equiv), THF–hexane, –78 °C, 1 h; (iv) CF_3CO_2Et (2 equiv), –78 °C to r.t., 1 h; (v) BCl_3 (1.5 equiv), CH_2Cl_2, –196 °C to r.t., 1 h.

Apart from the need for several steps because of the required protection/deprotection, as well as the only moderate overall yield of **3a** (35%), there is an additional serious limitation to this synthetic protocol. Obviously, it is not applicable to phenols with substituents in positions 3–5 that are sensitive towards nucleophilic attack. As for the second classical route to 2,6-diacylphenols, namely Prelog-type condensation,[8] the putative starting compound, 1,1,1,7,7,7-hexafluoroheptane-2,4,6-trione was synthesized only very recently.[9] Our first tests of its reactivity gave only disappointing results, and we therefore question the feasibility of this approach.

At the same time, there are some reports dealing with phenol formation via consecutive dehydrohalogenations in the cyclohexanone framework.[10] Indeed, in the course of recent work we observed that the 2,4-dibrominated 1,3,5-triketone **4b** underwent double dehydrobromination under basic conditions to afford phenol **3b** in 31% isolated yield (Table 1, entry 1).[11] Given the ease of the preparation of

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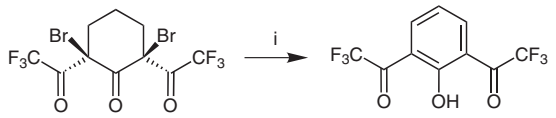
both compound **4b** and its precursor 2,6-bis(trifluoroacetyl)cyclohexanone (**5b**, Table 2),[12] we became interested to know whether related reactions could be developed into a general method to synthesize the target 2,6-bis(trifluoroacetyl)phenols **3** (Table 2). Attempts to directly convert **5b** into **3b** when conventional oxidants such as elemental sulfur or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone were used failed. On the other hand, we were pleased to find that the 1,3,5-triketone **4b**, pre-generated from **5b**, transformed into phenol **3b** spontaneously (Table 1, entry 2). There is no need to use any auxiliary reagents, although the dehydrobromination appeared to be sluggish at ambient temperature: the conversion is complete after 12 days, as indicated by ^{19}F NMR monitoring of the reaction mixture (Table 1, entry 2). Increase of the temperature accelerated the aromatization considerably, delivering compound **3b** in 82% yield after reflux for 40 hours in chloroform as reaction solvent (Table 1, entry 3). It is noteworthy that a further increase in reaction temperature did not lead to better results. When xylene was used instead of chloroform, the desired reaction was complicated by the formation of several unidentified side products.

Table 1 Dehydrobromination of Compound **4b**



4b **3b**

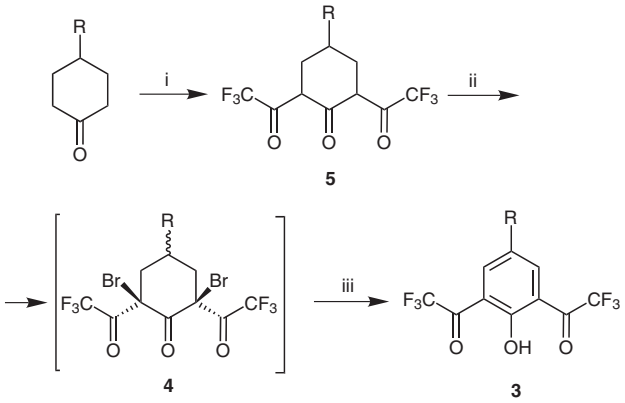
Entry	Reagents and conditions (i)	Isolated yield of **3b** (%)
1	Et_3N, CH_2Cl_2, –50 °C to r.t.	31[11]
2[a]	CH_2Cl_2, r.t., 12 d	67
3[a]	$CHCl_3$, reflux, 40 h	82

[a] Starting compound **4b** was pre-generated from **5b**,[11] and converted into **3b** without isolation.

With these results in hand and using the principles established earlier,[11] we were able to synthesize a range of phenol derivatives **3** with various substituents in the 4-position, starting from commercially available cyclohexanones. The corresponding synthetic sequence is depicted in Table 2. Double Claisen condensation with ethyl trifluoroacetate and with lithium hydride as the base provided the corresponding 1,3,5-triketones **5** in 70–90% yields (Table 2, step i). Treatment of **5** with excess elemental bromine furnished compounds **4** (Table 2, step ii),[11] which could be dehydrobrominated readily without isolation (step iii). This formal oxidation, or rather two-step aromatization of **5**, allowed the preparation of phenol derivatives **3** in a simple and convenient one-pot procedure in 51–95% yields (Table 2).

Within the substrates studied, the *tert*-butyl-substituted compound **4d** turned out to be the most reactive (Table 2). In this case, the dehydrobromination step did not require

Table 2 Synthesis of Phenols **3a–f** Starting from the Corresponding Cyclohexanones[a]



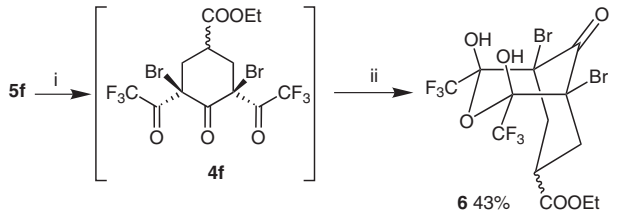
R	**5**	Yield[b] of **5** (%)	Intermediate **4**	Product **3**	Yield[b] of **3** (%)
Me	**5a**	82	**4a**	**3a**	92
H	**5b**	70	**4b**	**3b**	82
Pr	**5c**	73	**4c**	**3c**	95
t-Bu	**5d**	77	**4d**	**3d**[c]	61
Ph	**5e**	90	**4e**	**3e**	51
CO_2Et	**5f**	86	**4f**	**3f**	51
CO_2H	**5g**	85	**4g**	**3g**	–[d]

[a] Reagents and conditions: (i) LiH (2 equiv; 4 equiv for **5g**), CF_3CO_2Et (3 equiv), THF, reflux, 48–50 h; (ii) Br_2 (2 equiv), $CHCl_3$, r.t., 24–60 h; (iii) reflux, 20–60 h (except for **3d**).
[b] Isolated yield.
[c] Dehydrobromination step iii was carried out at r.t. (44 h).
[d] Formation of complex reaction mixtures, with product **3g** not detected at all.[14]

warming; product **3d** was obtained in 93% yield (by ^{19}F NMR) after 44 hours at ambient temperature.

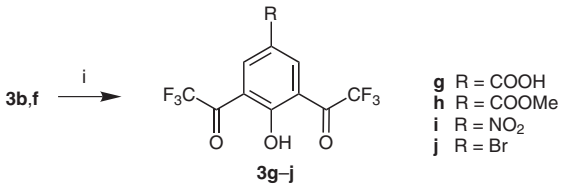
Dilution appears to play an important role in the course of this reaction. For instance, the attempted reaction of **5f** carried out in a reduced amount of chloroform as reaction medium gave the bridged compound **6**[13] repeatedly after workup (Scheme 2). When the amount of solvent was increased, it was possible to obtain **3f** in 51% yield (Table 2). The reason for this behavior of **4f** is not clear.

Since only complex reaction mixtures[14] formed when we tried to aromatize compound **5g** (Table 2), we sought to prepare acid **3g** from ester **3f** (Table 3). Potassium bicar-



Scheme 2 Formation of **6** from **5f**. *Reagents and conditions*: (i) Br_2 (2 equiv), $CHCl_3$, r.t., 20 h; (ii) reflux, 48 h.

Table 3 Synthesis of Compounds **3g–j** from **3b** and **3f**



Entry	Starting material	Reagents and conditions (i)	Product	Isolated yield (%)
1	**3f**	aq KOH, MeOH, r.t., 48 h	**3h**	53
2	**3f**	concd HCl, reflux, 10 h	**3g**	32
3	**3b**	HNO_3, H_2SO_4, –5 °C to 0 °C, 1 h	**3i**	73
4	**3b**	NBS (1.5 equiv), TFA, H_2SO_4, 0 °C to r.t., 2 h	**3j**[a]	23
5	**3b**	py (1.1 equiv), CH_2Cl_2, 0 °C, then Br_2 (1.1 equiv), r.t., 20 h	**3j**[a]	37
6	**3b**	py (1.1 equiv), CH_2Cl_2, –78 °C, then Br_2 (1.1 equiv), –78 °C, 30 min, then r.t., 16 h	**3j**[a]	57

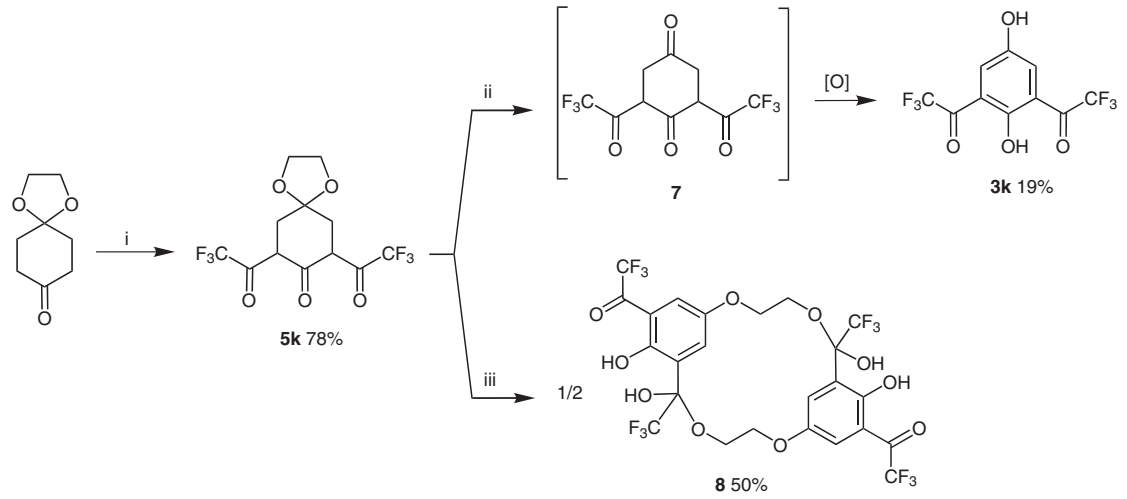
[a] 2,4-Dibromo-6-(trifluoroacetyl)phenol and 2,4,6-tribromophenol were detected as byproducts (see experimental section).

bonate in aqueous methanol[15] was investigated to no avail. Somewhat unexpectedly, when potassium bicarbonate was replaced by potassium hydroxide, trans-esterification of **3f** occurred to give methyl ester **3h** as the sole isolable product (Table 3, entry 1). The saponification of **3f** could be achieved under harsh acidic conditions, furnishing acid **3g** in moderate yield (Table 3, entry 2).

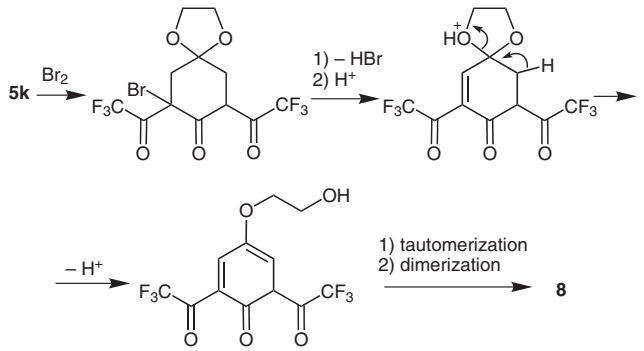
To achieve further functionalization of the 4-position in the 2,6-bis(trifluoroacetyl)phenol molecule, we studied the behavior of parent compound **3b** in aromatic electrophilic substitution reactions (Table 3, entries 3–6). Nitration of **3b** proceeded smoothly, yielding **3i** in 73% yield (Table 3, entry 3). The bromination reaction appeared to be more delicate, and we therefore examined several reaction conditions for it (Table 3, entries 4–6). Under neutral conditions, phenol **3b** showed no reactivity towards bromine. This can be explained by the electron-withdrawing influence of the two trifluoroacetyl groups, which reduces the nucleophilicity of the phenol ring. An attempt with a bromonium reagent, pre-generated from *N*-bromosuccinimide in trifluoroacetic acid–sulfuric acid,[16] delivered 4-bromophenol **3j** in 23% yield (Table 3, entry 4). The better results were obtained from the reaction between a pyridinium salt of **3b** and bromine, performed at –78 °C to 20 °C (Table 3, entries 5 and 6). It should be noted that the products of a further bromination, namely 2,4-dibromo-6-(trifluoroacetyl)phenol and 2,4,6-tribromophenol, were detected in small amounts in these reactions (Table 3, entries 4–6).

With 1,3,5-triketone **5k** obtained from mono-protected cyclohexane-1,4-dione (Scheme 3), the synthesis of 2,6-bis(trifluoroacetyl)-1,4-benzoquinone and 2,6-bis(trifluoroacetyl)-1,4-hydroquinone (**3k**) was envisaged. Aqueous formic acid in toluene, which had been reported to be an extremely efficient reagent to remove the ethylene glycol protection group from cyclohexanone,[17] did not work at all in our case. To our surprise, treatment of **5k** with hydrochloric acid gave 1,4-hydroquinone **3k** directly (Scheme 3). One can assume that the deprotection step is followed by oxidation of the intermediary tetraketone **7** with air oxygen in this case. It is worth mentioning that the formation of the corresponding 1,4-benzoquinone was not detected. When subjected to bromination, **5k** yielded a yellow crystalline material only poorly soluble in deuterated chloroform and deuterated acetonitrile. Unfortunately, when dissolved in more polar solvents (acetone-d_6, DMSO-d_6, THF-d_8), it appeared to be unstable, and all attempts to grow single crystals suitable for X-ray diffraction analysis failed. Nevertheless, on the basis of elemental analysis data as well as ^{1}H and ^{19}F NMR spectra recorded in various solvents, the macrocyclic structure **8** could be suggested (Scheme 3). The probable mechanism of aromatization involves a bromination–dehydrobromination–elimination–tautomerization sequence (Scheme 4). The driving force of the dimerization into bis-hemiketal **8** is obviously the increased electrophilicity of the trifluoroacetyl moieties: the ability of the strong electron-withdrawing trifluoromethyl group[18] to stabilize the adjacent hemiketal center is well known.[9,11]

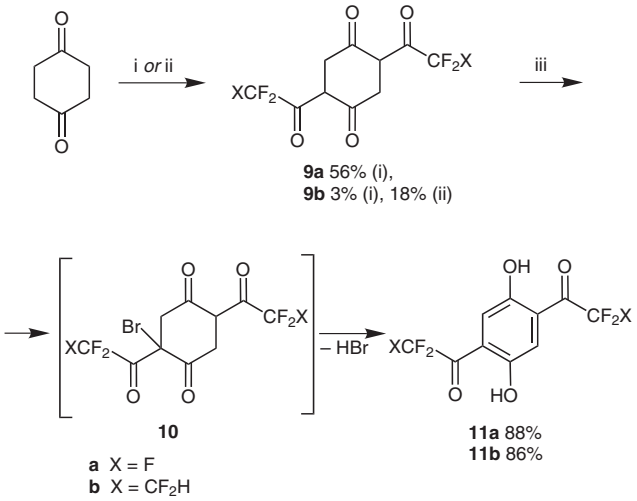
As an extension of these studies, the synthesis of 1,4-hydroquinones **11** bearing the fluoroacyl moieties in positions 2 and 5 was undertaken. On the basis of published data concerning closely related succinyl succinates,[19] and the results above, tetraketones **9** were chosen as precursors of **11** (Scheme 5). Double trifluoroacetylation of cyclohexane-1,4-dione with ethyl trifluoroacetate and sodium methoxide as base yielded **9a** in 56% yield (Scheme 5). Application of this procedure for double Claisen condensation with methyl 2,2,3,3-tetrafluoropropionate gave tetraketone **9b** in only 3% yield. When lithium diisopro-



Scheme 3 Synthesis and aromatization of 1,3,5-triketone **5k**. *Reagents and conditions*: (i) LiH (2.2 equiv), CF_3CO_2Et (3 equiv), THF, reflux, 48 h; (ii) concd HCl, MeOH, reflux, 2 h, then r.t., 15 h; (iii) Br_2 (2.2 equiv), $CHCl_3$, r.t., 48 h.



Scheme 4 Possible mechanism of the formation of dimer **8** from **5k**



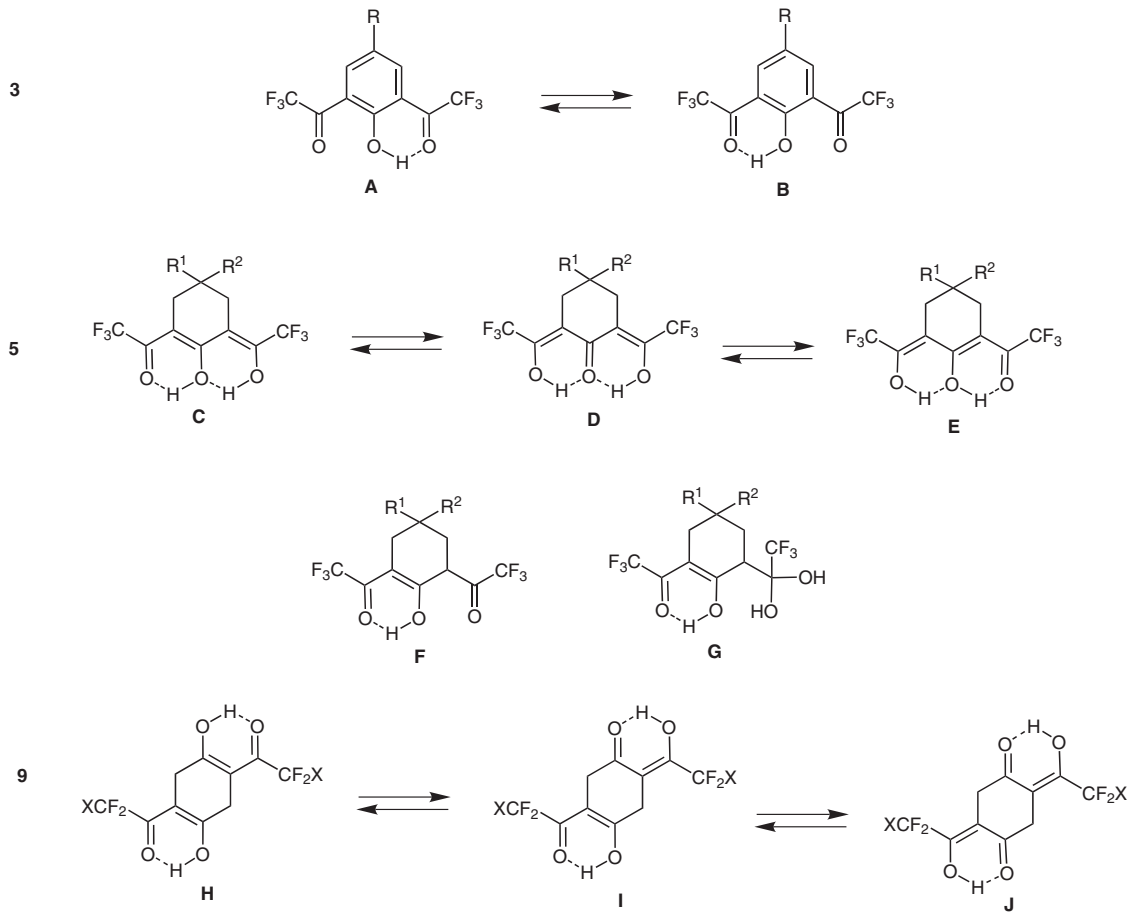
Scheme 5 Synthesis of 1,4-hydroquinones **11**. *Reagents and conditions*: (i) NaOMe (2.2 equiv), XCF_2CO_2R (2.1 equiv), Et_2O, 24 h; (ii) LDA (2 equiv), $HCF_2CF_2CO_2Me$ (2 equiv), THF, –78 °C, then r.t., 12 h; (iii) Br_2 (1 equiv), $CHCl_3$, r.t., 10 h.

pylamide was used as the base instead of sodium methoxide, the yield of **9b** could be somewhat improved to 18% (Scheme 5). The aromatization of compounds **9** proceeded smoothly: upon treatment with elemental bromine, 1,4-hydroquinones **11a** and **b** were obtained in 88% and 86% yield, respectively (Scheme 5). In contrast to the reaction of **5** (Scheme 3), one equivalent of bromine is sufficient for the aromatization of **9** (Scheme 5). Indeed, the elimination of hydrogen bromide from the mono-α-brominated intermediate **10** followed by redistribution of the double bonds in the ring via keto enol and dienone–phenol tautomerism gave rise to the aromatic ring, as shown in Scheme 5.

The structural features of the di-, tri-, and tetracarbonyl compounds obtained require special comments (Scheme 6). According to the NMR spectroscopy data collected for deuterated chloroform and acetone-d_6 solutions at room temperature (see experimental section), phenols **3** have a *symmetrical* structure, although the δ_H range (11.1–12.4) of the phenolic hydroxy proton verifies the presence of the hydrogen bond. Presumably, this hydrogen bond simultaneously involves two trifluoroacetyl functions with the single phenolic hydroxy group (Scheme 6). The energy barrier between the two forms **A** and **B** (Scheme 6) seems to be low, and, therefore, the hydroxy proton 'jumps' between the two carbonyl oxygens giving rise to a 'bifurcate' hydrogen-bonded structure (Scheme 6). This process is rapid on the NMR timescale at room temperature, resulting in an averaged spectrum.[20,21]

Analogously to other fluorinated 1,3,5-triketones,[12,22] the bis-enol is the predominant species for compounds **5** in deuterated chloroform, acetone-d_6, and tetrahydrofuran solutions at room temperature, as confirmed by ^1H and ^{19}F NMR spectroscopy. Due to the fast 'enol–enol' tautomerism **C** ⇆ **D** ⇆ **E** (Scheme 6)[12,20,22] only an averaged set of signals is evident for this tautomer. The less abundant mono-enol form **F** as well as monohydrate (*gem*-diol) **G** were also observed (Scheme 6).

In deuterated chloroform solution at room temperature, complete enolization was established for both compounds



Scheme 6 Hydrogen bonding and enolization features of compounds **3**, **5**, and **9**

9a,**b** by ^{1}H and ^{19}F NMR spectroscopy, within the limits of detection. The fast 'enol–enol' tautomerism[20,22,23] manifests itself by the sole averaged set of signals, including resonances of two hydroxy protons [δ_H = 14.57 (**9a**), 15.04 (**9b**)] and C(3,6)H_2 groups [δ_H = 3.60 (**9a**), 3.68 (**9b**)], as well as resonances of polyfluoroalkyl moieties. The $^3J_{H,F}$ coupling constant of CF_2H in **9b** is 5.3 Hz; this suggests that the bis-*endo*-enol form **H** is a predominant tautomeric form in deuterated chloroform solution,[24] rather than *exo*-*endo*-bis-enol **I** or bis-*exo*-enol **J** (Scheme 6).

An additional NMR feature of compounds **3**, **5**, **9**, and **11** should be mentioned, namely that $^4J_{C,F}$ and $^5J_{H,F}$ splitting is observed. This splitting, probably resulting from through-space coupling, is in good accordance with the U-type structure[25] of the intramolecularly hydrogen-bonded species under discussion.

To summarize, a simple, efficient, and convenient method to synthesize 2,6-bis(trifluoroacetyl)phenols was developed, involving aromatization of 2,6-bis(trifluoroacetyl)cyclohexanones by a one-pot dibromination–double dehydrobromination procedure. Application of this approach to cyclohexane-1,4-dione as well as 4-position functionalization of the parent 2,6-bis(trifluoroacetyl)phenol opened access to valuable fluoroacylated phenols and 1,4-hydroquinones, which are not easily obtained by other methods. Structural features of these compounds were studied by multinuclear NMR spectroscopy; this established the presence of a 'bifurcate' intramolecular hydrogen bond in 2,6-bis(trifluoroacetyl)phenols as well as predominant U-bis-enolization of their 1,3,5-tricarbonyl precursors and 2,5-bis(polyfluoroacyl)cyclohexane-1,4-diones.

Melting and boiling points are uncorrected. ^{1}H (200 MHz), ^{13}C (50 MHz), and ^{19}F (188 MHz) NMR spectra were recorded at 22 °C on a Bruker DPX-200 spectrometer scaled to TMS (^{1}H and ^{13}C) and CCl_3F (^{19}F). NMR chemical shifts are referenced with respect to the residual solvent signals (^{1}H: δ = 7.25, 2.05, 1.73 for $CDCl_3$, acetone-d_6, THF-d_8, respectively; ^{13}C: δ = 77.0 and 29.9 for $CDCl_3$ and acetone-d_6, respectively). Reaction progress was monitored by ^{19}F NMR spectroscopy for samples from the reaction mixtures dissolved in $CHCl_3$ containing hexafluorobenzene as an internal reference (without lock). Signals in the ^{13}C NMR spectra of compounds **3c**,**e**,**j**,**k** were assigned on the basis of DEPT135 experiments, as well as on $^4J_{C,F}$ splitting. Signals of the CF_2 moieties in the ^{13}C NMR spectrum of compound **11b** were assigned on the basis of an HSQC experiment. MS was carried out by EI (70 eV) on a Finnigan MAT-8200 and MAT-95 spectrometers, and by CI (NH_3 as reactant gas) on a MAT-8200 spectrometer. HRMS was carried out by the peak matching method on a Finnigan MAT-95 spectrometer. Elemental analyses were carried out by the Microanalytisches Beller Labor, Göttingen, Germany. $CHCl_3$ for brominations was purchased from Fisher Scientific and used without further purification. 4-Oxocyclohexanecarboxylic acid was prepared according to a literature method.[26] 2,6-Dibromo-4-methylanisole (**1**) was prepared by methyl-

ation of sodium 2,6-dibromo-4-methylphenolate with dimethyl sulfate according to a published procedure.[27] Other chemicals are commercially available and were used as purchased unless otherwise specified. Reactions in anhyd solvents ($CHCl_3$ and CH_2Cl_2 from P_2O_5; Et_2O and THF from sodium/benzophenone ketyl) were performed in oven-dried glassware under a static N_2 atmosphere. Silica gel grade 60, 320–630 mesh (MP Biomedicals Germany GmbH) was used for column chromatography.

2,6-Bis(trifluoroacetyl)cyclohexanones 5a–f,k; General Procedure

A soln of the appropriate cyclohexanone (86 mmol) and CF_3CO_2Et (36.7 g, 256 mmol) in anhyd THF (100 mL) was added dropwise to a well-stirred suspension of finely powdered LiH (1.5 g, 189 mmol) in THF (150 mL). After complete addition, the mixture was heated at reflux for 48 h and then cooled to r.t.; ca. 100 mL of solvent was evaporated. Then 10% aq H_2SO_4 (190 mL) was added carefully to the residue, and the mixture was stirred for 10 min and then extracted with Et_2O (5 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was distilled in vacuo. 1,3,5-Triketones **5b** (70%),[12] **5d** (77%),[11] and **5e** (90%),[22] obtained according to this general procedure, are known compounds.

4-Methyl-2,6-bis(trifluoroacetyl)cyclohexanone (5a)

Yield: 82%; yellow liquid; bp 128–132 °C/20 Torr.

Exists in $CDCl_3$ soln as a mixture of bis-enol, mono-enol **F**, and mono-hydrate (*gem*-diol) **G** (88:6:6; by NMR).[28]

MS (EI, 70 eV): *m*/*z* (%) = 304 (52) $[M]^+$, 235 (100) $[M - CF_3]^+$, 165 (10) $[M - 2\,CF_3 - H]^+$.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{11}H_{10}F_6O_3$: 304.0534; found: 304.0537; –1.0 ppm, –0.3 mu, $R \approx 10000$.

Bis-enol Form of 5a

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.07 (d, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3), 1.70–1.96 (m, 1 H, 4-H), 2.06–2.19 (m, 2 H, 3,5-H), 2.62–2.70 (m, 2 H, 3,5-H), 14.6 (br s, 2 H, 2 × OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –68.75 (dt, $^4J_{F,H}$ = 2.0, $^5J_{F,H}$ = 1.4 Hz, CF_3).

Mono-enol F Form of 5a

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.05 (dd, $^3J_{H,H}$ = 7.1, $^3J_{H,H}$ = 2.4 Hz, 1 H, 2-H), other signals are overlapped by more intensive signals of the most abundant tautomer.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –77.52 [s, 3 F, $C(O)CF_3$], –73.99 (unresolved td, $^5J_{F,H} \approx 0.9$, $^4J_{F,H} \approx 0.5$ Hz, $=CCF_3$).

Mono-hydrate G Form of 5a

^{19}F NMR (188 MHz, $CDCl_3$): δ = –78.53 [s, 3 F, $C(OH)_2CF_3$], –73.68 (m, 3 F, $=CCF_3$).

4-Propyl-2,6-bis(trifluoroacetyl)cyclohexanone (5c)

Yield: 73%; yellow liquid; boiling interval 140–146 °C/12 Torr.

Exists in $CDCl_3$ soln as a mixture of bis-enol, mono-enol **F**, and mono-hydrate (*gem*-diol) **G** (53:24:23; by NMR).[28]

MS (EI, 70 eV): *m*/*z* (%) = 332 (52) $[M^+]$, 313 (9) $[M - F]^+$, 289 (11) $[M - C_3H_7]^+$, 263 (100) $[M - CF_3]^+$, 236 (18) $[M - CF_3CO + H]^+$, 69 (22) $[CF_3^+]$, 41 (33) $[C_3H_5^+]$.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}F_6O_3$: 332.0847; found: 332.0848; –0.4 ppm, –0.1 mu, $R \approx 10000$.

Bis-enol Form of 5c

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.93 (t, $^3J_{H,H}$ = 6.4 Hz, 3 H, CH_3), 1.24–1.46 (m, 4 H, $CH_2CH_2CH_3$), 1.63–1.76 (m, 1 H, 4-H), 2.15 (dd, 2 H, 3,5-H, $^2J_{H,H}$ = 15.4, $^3J_{H,H}$ = 10.4 Hz), 2.64–2.71 (m, 2 H, 3,5-H), 14.6 (br s, 2 H, 2 × OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –68.70 (dt, $^4J_{F,H}$ = 1.6, $^5J_{F,H}$ = 0.5 Hz, CF_3).

Mono-enol F Form of 5c

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.05 (dd, $^3J_{H,H}$ = 5.9, $^3J_{H,H}$ = 3.4 Hz, 1 H, 2-H), 14.3 (br s, 1 H, OH), other signals are overlapped by more intensive signals of the most abundant tautomer.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –77.39 [s, 3 F, $C(O)CF_3$], –73.91 (dt, $^5J_{F,H}$ = 1.1 Hz, 3 F, $=CCF_3$).

Mono-hydrate G Form of 5c

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.10–4.15 (m, 1 H, 2-H), 14.5 (br s, 1 H, OH), other signals are overlapped by more intensive signals of the most abundant tautomer.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –78.49 [s, 3 F, $C(OH)_2CF_3$], –73.65 (m, 3 F, $=CCF_3$).

Ethyl 4-Oxo-3,5-bis(trifluoroacetyl)cyclohexanecarboxylate (5f)

Yield: 86%; yellow liquid; boiling interval 90–105 °C/0.5 Torr.

Exists in $CDCl_3$ soln as a mixture of bis-enol, mono-enol **F**, and mono-hydrate (*gem*-diol) **G** (89:6:5; by NMR).[28]

MS (EI, 70 eV): *m*/*z* (%) = 362 (54) $[M^+]$, 342 (59) $[M - HF]^+$, 317 (10) $[M - OC_2H_5]^+$, 293 (12) $[M - CF_3]^+$, 289 (56) $[M - CO_2C_2H_5]^+$, 269 (35) $[M - HF - CO_2C_2H_5]^+$, 219 (100) $[M - CF_3 - CO_2C_2H_5 - H]^+$, 69 (20) $[CF_3^+]$, 29 (50) $[C_2H_5^+]$.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}F_6O_5$: 362.0589; found: 362.0583; 1.8 ppm, 0.6 mu, $R \approx 10000$.

Bis-enol Form of 5f

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, CH_3), 2.68–2.91 (m, 5 H, 1,2,6-H), 4.16 (q, $^3J_{H,H}$ = 7.3 Hz, 2 H, OCH_2), 14.68 (q, $^4J_{H,F}$ = 2.1 Hz, 2 H, 2 × OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –68.87 (m, CF_3).

Mono-enol F Form of 5f

^{1}H NMR (200 MHz, $CDCl_3$): δ = 14.25 (s, 1 H, OH), other signals are overlapped by more intensive signals of the most abundant tautomer.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –78.11 [s, 3 F, $C(O)CF_3$], –74.08 (t, $^5J_{F,H}$ = 1.0 Hz, 3 F, $=CCF_3$).

Mono-hydrate G Form of 5f

^{1}H NMR (200 MHz, $CDCl_3$): δ = 14.42 (s, 1 H, OH), other signals are overlapped by more intensive signals of the most abundant tautomer.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –78.42 [s, 3 F, $C(OH)_2CF_3$], –73.94 (m, 3 F, $=CCF_3$).

7,9-Bis(trifluoroacetyl)-1,4-dioxaspiro[4.5]decan-8-one (5k)

Yield: 78%; yellow liquid which solidified quickly; boiling interval 101–108 °C/1 Torr, melting interval 41–46 °C.

Exists in $CDCl_3$ soln as a mixture of bis-enol and mono-enol **F** (87:13; by NMR).[28]

MS (EI, 70 eV): *m*/*z* (%) = 348 (55) $[M^+]$, 330(10) $[M - H_2O]^+$, 279 (40) $[M - CF_3]^+$, 251 (15) $[M - CF_3CO]^+$, 86 (100) $[C_4H_6O_2^+]$.

HRMS: *m*/*z* $[M]^+$ calcd for $C_{12}H_{10}F_6O_5$: 348.0432; found 348.0437; –1.3 ppm, –0.4 mu, $R \approx 10000$.

Bis-enol Form of 5k

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.69 (s, 4 H, 3,5-H), 4.00 (s, 4 H, OCH_2CH_2O), 14.59 (q, $^4J_{H,F}$ = 1.9 Hz, 2 H, 2 × OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –68.90 (td, $^5J_{F,H}$ = 1.9, $^4J_{F,H}$ = 1.6 Hz, CF_3).

Mono-enol F Form of 5k

^{1}H NMR (200 MHz, $CDCl_3$): δ = 14.6 (br s, 1 H, OH), other signals are overlapped by more intensive signals of the most abundant tautomer.

^{19}F NMR (188 MHz, $CDCl_3$): δ = –77.52 [s, 3 F, $C(O)CF_3$], –73.85 (t, $^5J_{F,H}$ = 1.2 Hz, 3 F, $=CCF_3$).

4-Oxo-3,5-bis(trifluoroacetyl)cyclohexanecarboxylic Acid (5g)

A soln of 4-oxocyclohexanecarboxylic acid (0.56 g, 3.9 mmol) and CF_3CO_2Et (1.70 g, 11.8 mmol) in anhyd THF (10 mL) was added dropwise to a well-stirred suspension of finely powdered LiH (0.13 g, 15.8 mmol) in THF (20 mL). The mixture was heated at reflux for 50 h and cooled to r.t.; the precipitated solid was collected by filtration, washed with PE, and dried. To a well-stirred suspension of this solid in Et_2O (10 mL) was added 10% aq H_2SO_4 (16 mL). The mixture was stirred for 10 min, and the organic layer was separated. After additional extraction of the mixture with Et_2O (2 × 10 mL), the combined organic phases were dried ($MgSO_4$) and concentrated; this gave a brown liquid, which solidified. Recrystallization from toluene gave **5g** as yellowish crystals. The bis-enol, mono-enol **F**, and mono-hydrate (*gem*-diol) **G** forms were detected in acetone-d_6 and THF solns by NMR spectroscopy [88:6:6 (acetone-d_6), 91:5:4 (THF)].[28]

Yield: 1.1 g (85%); mp 142–144 °C.

MS (EI, 70 eV): *m/z* (%) = 334 (100) [M$^+$], 316 (32) [M – H_2O]$^+$, 289 (16) [M – CO_2H]$^+$, 265 (44) [M – CF_3]$^+$, 219 (80) [M – CO_2H – CF_3 – H]$^+$, 191 (89) [M – CF_3CO – CO_2H – H]$^+$.

HRMS: *m/z* [M]$^+$ calcd for $C_{11}H_8F_6O_5$: 334.0276; found 334.0283; –2.2 ppm, –0.7 mu, $R \approx 10000$.

Bis-enol Form of 5g

^{1}H NMR (200 MHz, acetone-d_6): δ = 2.76–3.01 (m, 5 H, 1,2,6-H), 11.1 (br s, 1 H, CO_2H), 14.6 (br s, 2 H, 2 × OH).

^{19}F NMR (188 MHz, acetone-d_6): δ = –69.53 (s, CF_3).

^{19}F NMR (188 MHz, THF, without lock): δ = –70.0 (s, CF_3).

Mono-enol F Form of 5g

^{1}H NMR (200 MHz, acetone-d_6): δ = 4.59 (t, $^3J_{H,H}$ = 6.6, Hz, 1 H, 5-H), other signals are overlapped by more intensive signals of the most abundant tautomer.

^{19}F NMR (188 MHz, acetone-d_6): δ = –78.64 [s, 3 F, $C(O)CF_3$], –74.20 (s, 3 F, $=CCF_3$).

^{19}F NMR (188 MHz, THF, without lock): δ = –79.3 [s, 3 F, $C(O)CF_3$], –74.8 (s, 3 F, $=CCF_3$).

Mono-hydrate G Form of 5g

^{1}H NMR (200 MHz, acetone-d_6): δ = 4.73 (dd, $^3J_{H,H}$ = 10.8, $^3J_{H,H}$ = 6.4 Hz, 1 H, 2-H), 6.64 (s, 2 H, 2 × OH), other signals are overlapped by more intensive signals of the most abundant tautomer.

^{19}F NMR (188 MHz, acetone-d_6): δ = –79.04 [s, 3 F, $C(OH)_2CF_3$], –73.81 (m, 3 F, $=CCF_3$).

^{19}F NMR (188 MHz, THF, without lock): δ = –79.7 [s, 3 F, $C(O)CF_3$], –74.6 (s, 3 F, $=CCF_3$).

2,6-Bis(trifluoroacetyl)phenols 3a–c,f from the Corresponding 2,6-Bis(trifluoroacetyl)cyclohexanones 5a–c,f; General Procedure

A soln of Br_2 (16.0 g, 100 mmol) in $CHCl_3$ (30 mL) was added dropwise to a well-stirred soln of the appropriate **5** (50 mmol) in $CHCl_3$ (200 mL) at r.t. The resulting red soln was stirred for 24 h (**3f**), 42 h (**3b**), or 60 h (**3a**,**c**) at r.t., and then heated at reflux for an additional 20 h (**3a**), 40 h (**3b**), or 60 h (**3c**,**f**), depending on the reaction progress, as determined by ^{19}F NMR monitoring of the reaction mixture. After the volatile materials had been removed in vacuo, the residue was purified by recrystallization or distillation.

4-Methyl-2,6-bis(trifluoroacetyl)phenol (3a)

Yield: 92%; yellowish crystals; mp 51–52 °C (hexane).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H, CH_3), 7.88 (s, 2 H, 3,5-H), 11.74 (s, 1 H, OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 20.3 (s, CH_3), 115.9 (q, $^1J_{C,F}$ = 290.1 Hz, CF_3), 118.5 (s, 2,6-C), 129.8 (s, 4-C), 138.9 (q, $^4J_{C,F}$ = 2.4 Hz, 3,5-H), 162.2 (s, 1-C), 182.8 [q, $^2J_{C,F}$ = 37.0 Hz, $C(O)CF_3$].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.75 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 300 (25) [M$^+$], 281 (1) [M – F]$^+$, 231 (100) [M – CF_3]$^+$, 161 (38) [M – 2 CF_3 – H]$^+$.

Anal. Calcd for $C_{11}H_6F_6O_3$: C, 44.02; H, 2.01; F 38.0. Found: C, 44.24; H, 2.01; F, 38.1.

2,6-Bis(trifluoroacetyl)phenol (3b)

Yield: 82%; yellow liquid; boiling interval 118–130 °C/12 Torr.

In contrast to **3b** described earlier,[11] the mono-hydrate (i.e., *gem*-diol) was not detected by NMR spectroscopy. Alternatively, **3b** could be prepared in 67% yield (Table 1, entry 2). Performed in CH_2Cl_2 at r.t., dehydrobromination of 2,4-dibromo-1,3,5-triketone **4b** (pregenerated from **5b** and 2 equiv Br_2) was complete after 12 d, as determined by ^{19}F NMR monitoring of the reaction mixture. Aqueous workup followed by column chromatography ($CHCl_3$) gave **3b** as a mixture with its mono-hydrate (68:32; by NMR).

4-Propyl-2,6-bis(trifluoroacetyl)phenol (3c)

Yield: 95%; red liquid; boiling interval 82–94 °C/1 Torr.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H, CH_3), 1.56–1-75 (m, 2 H, CH_2CH_3), 2.64 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, $ArCH_2$), 7.87 (s, 2 H, 3,5-H), 11.75 (s, 1 H, OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 13.4 (s, CH_3), 24.2 (s, CH_2CH_3), 36.7 (s, $ArCH_2$), 116.0 (q, $^1J_{C,F}$ = 290.6 Hz, CF_3), 118.5 (s, 2,6-C), 134.5 (s, 4-C), 138.3 (s, 3,5-C), 162.3 (s, 1-C), 182.8 [q, $^2J_{C,F}$ = 37.2 Hz, $C(O)CF_3$].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.73 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 328 (24) [M$^+$], 299 (22) [M – C_2H_5]$^+$, 259 (100) [M – CF_3]$^+$, 229 (19) [M – C_2H_5 – CF_3]$^+$, 189 (10) [M – 2 CF_3 – H]$^+$.

HRMS: *m/z* [M]$^+$ calcd for $C_{13}H_{10}F_6O_3$: 328.0534; found: 328.0524; 3.1 ppm, 1.0 mu, $R \approx 10000$.

4-Ethyl 4-Hydroxy-3,5-bis(trifluoroacetyl)benzoate (3f)

Yield: 51%; yellow crystals; mp 68–69 °C (heptane–toluene, 5:1).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3), 4.43 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2), 8.74 (s, 2 H, 2,6-H), 12.17 (s, 1 H, OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 14.2 (s, CH_3), 62.2 (s, CH_2), 115.7 (q, $^1J_{C,F}$ = 289.6 Hz, CF_3), 118.7 (s, 3,5-C), 123.0 (s, 1-C), 139.3 (unresolved q, $^4J_{C,F} \approx 2.8$ Hz, 2,6-C), 163.3 (s, 4-C), 166.3 (s, $CO_2C_2H_5$), 182.7 [q, $^2J_{C,F}$ = 38.1 Hz, $C(O)CF_3$].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.90 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 358 (6) [M^+], 313 (18) [M – C_2H_5O]$^+$, 289 (100) [M – CF_3]$^+$, 261 (40) [M – CF_3CO]$^+$, 243 (13) [M – C_2H_5O – CF_3 – H]$^+$, 216 (7) [M – C_2H_5O – CF_3CO]$^+$, 191 (40) [M – CF_3CO – CF_3 + H]$^+$, 165 (6) [M – 2 CF_3CO + H]$^+$, 119 (8) [M – C_2H_5O – 2 CF_3CO]$^+$, 91 (17) [M – 2 CF_3CO – $CO_2C_2H_5$]$^+$, 73 (2) [$CO_2C_2H_5^+$], 69 (9) [CF_3^+], 29 (10) [$C_2H_5^+$].

HRMS: *m/z* [M]$^+$ calcd for $C_{13}H_8F_6O_5$: 358.0276; found: 358.0276; 0.1 ppm, 0.0 mu, $R \approx 10000$.

4-(*tert*-Butyl)-2,6-bis(trifluoroacetyl)phenol (3d)

Br_2 (0.51 g, 3.2 mmol) was added dropwise to a well-stirred soln of the 1,3,5-triketone **5d** (0.50 g. 1.4 mmol) in $CHCl_3$ (5 mL) at r.t. The resulting red soln was stirred for 44 h at r.t. After the reaction was complete (^{19}F NMR monitoring), the volatile materials were removed in vacuo to leave a yellow semi-solid. Column chromatography ($CHCl_3$) yielded the product. Besides **3d**, its mono-hydrate (13%)[28] was detected by NMR spectroscopy.

Yield: 0.30 g (61%); yellow oil.

MS (EI, 70 eV): *m/z* (%) = 342 (12) [M^+], 327 (100) [M – CH_3]$^+$, 273 (20) [M – CF_3]$^+$.

HRMS: *m/z* [M]$^+$ calcd for $C_{14}H_{12}F_6O_3$: 342.0691; found: 342.0695; –1.3 ppm, –0.4 mu, $R \approx 9000$.

3d (A ⇆ B)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, *t*-Bu), 8.10 (s, 2 H, 3,5-H), 11.72 (s, 1 H, OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 30.8 (s, CH_3), 34.5 [s, $C(CH_3)_3$], 116.0 (q, $^1J_{C,F}$ = 290.1 Hz, CF_3), 118.3 (s, 2,6-C), 135.7 (s, 3,5-C), 143.2 (s, 4-C), 162.0 (s, 1-C), 183.0 [q, $^2J_{C,F}$ = 37.2 Hz, C(O)CF_3].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.72 (s, CF_3).

Mono-hydrate Form of 3d

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 9 H, *t*-Bu), 4.9 (br s, 2 H, 2 × OH), 7.89–7.96, 8.12–8.18 (both m, 2 × 1 H, 3,5-H), 12.07 (s, 1 H, 1-OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –86.10 [s, 3 F, $C(OH)_2CF_3$], –70.49 [d, 3 F, $^5J_{F,H}$ = 2.0 Hz, 3 F, C(O)CF_3].

4-Phenyl-2,6-bis(trifluoroacetyl)phenol (3e)

A soln of Br_2 (14.9 g, 92 mmol) in $CHCl_3$ (30 mL) was added dropwise to a well-stirred soln of the 1,3,5-triketone **5e** (17.0 g. 46 mmol) in $CHCl_3$ (250 mL) at r.t. The resulting red soln was stirred for 60 h at r.t., and then heated at reflux for 20 h (^{19}F NMR monitoring of the reaction mixture). The mixture was cooled to r.t., and another portion of Br_2 (3.7 g, 23 mmol) was added. After further stirring of the mixture for 20 h at r.t., the volatile materials were removed in vacuo. The orange oily residue was dissolved in hexane and cooled to –30 °C; this caused a precipitate to form. The product was collected by filtration and recrystallized from hexane.

Yield: 8.5 g (51%); yellow crystals; mp 76–77 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40–7.60 (m, 5 H, C_6H_5), 8.28 (s, 2 H, 3,5-H), 11.86 (s, 1 H, OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 116.0 (q, $^1J_{C,F}$ = 290.1 Hz, CF_3), 119.1 (s, 2,6-C), 126.8, 128.6, 129.4, 133.8 (s, C_6H_5), 137.4 (s, 4-C), 136.8 (q, $^4J_{C,F}$ = 1.9 Hz, 3,5-C), 163.0 (s, 1-C), 183.9 [q, $^2J_{C,F}$ = 37.2 Hz, C(O)CF_3].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.68 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 362 (88) [M^+], 293 (100) [M – CF_3]$^+$, 223 (28) [M – 2 CF_3 – H]$^+$, 168 (10) [M – 2 CF_3CO]$^+$, 77 (3) [$C_6H_5^+$], 69 (8) [CF_3^+].

HRMS: *m/z* [M]$^+$ calcd for $C_{16}H_8F_6O_3$: 362.0378; found: 322.0376; 0.6 ppm, 0.2 mu, $R \approx 10000$.

4-Bromo-2,6-bis(trifluoroacetyl)phenol (3j) by Aromatization of 1,3,5-Triketone 5g

Br_2 (0.71 g, 4.5 mmol) was added dropwise to a well-stirred soln of **5g** (0.48 g, 1.4 mmol) in $CHCl_3$ (10 mL) at r.t. The resulting red soln was stirred for 36 h at r.t. and then heated at reflux for an additional 40 h. ^{19}F NMR monitoring of the reaction mixture revealed a complex mixture of several aromatic products in approximately equal concentrations. The mixture was cooled to r.t., and H_2O (5 mL) was added. After the mixture had stirred for 2 h at r.t., additional H_2O (20 mL) was added and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 × 15 mL), and the combined organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow semi-solid. Column chromatography (EtOAc) allowed the isolation of bis(trifluoroacetyl)phenol **3j** as a mixture with the corresponding mono-hydrate (47:53,[28] by NMR), and 2,4-dibromo-6-(trifluoroacetyl)phenol.

4-Bromo-2,6-bis(trifluoroacetyl)phenol (3j)

Yield: 60 mg (13%); yellow solid; melting interval 71–78 °C.

MS (CI, positive): *m/z* (%) = 364 (66) [M^+], 344 (100) [M – HF]$^+$.

MS (EI, 70 eV): *m/z* = 382 (1) [M + H_2O]$^+$, 364 (27) [M^+], 295 (100) [M – CF_3]$^+$, 275 (8) [M – CF_3 – HF]$^+$, 225 (48) [M – 2 CF_3 – H]$^+$, 197 (6) [M – CF_3 – CF_3CO – H]$^+$, 28 (24) [CO^+].

HRMS: *m/z* [M]$^+$ calcd for $C_{10}H_3{}^{79}BrF_6O_3$: 363.9170; found: 363.9173; –0.9 ppm, 0.3 mu, $R \approx 10000$.

3j (A ⇆ B)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.15 (s, 2 H, 3,5-H), 11.8 (br s, 1 H, OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 115.7 (q, $^1J_{C,F}$ = 289.9 Hz, CF_3), 120.3 (s, 2,6-C), 126.6 (s, 4-C), 140.6 (q, $^4J_{C,F}$ = 2.9 Hz, 3,5-C), 162.5 (s, 1-C), 182.1 [q, $^2J_{C,F}$ = 38.0 Hz, C(O)CF_3].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.95 (s, CF_3).

Mono-hydrate Form of 3j

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.9 (br s, 2 H, 2 × OH), 8.01–8.06 (m, 1 H, 3-H), 8.19 (d, $^4J_{H,H}$ = 2.6 Hz, 1 H, 5-H), 12.1 (s, 1 H, 1-OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 97.1 [q, $^2J_{C,F}$ = 34.7 Hz, $C(OH)_2CF_3$], 112.9, 115.4 (both s, 2-C, 6-C), 115.9 [q, $^1J_{C,F}$ = 289.5 Hz, C(O)CF_3], 122.6 [q, $^1J_{C,F}$ = 289.0 Hz, $C(OH)_2CF_3$], 126.6 (s, 4-C), 135.0 (q, $^4J_{C,F}$ = 3.7 Hz, 3-C), 142.5 (s, 5-C), 160.0 (s, 1-C), 184.6 [q, $^2J_{C,F}$ = 36.8 Hz, C(O)CF_3].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –85.81 [s, 3 F, $C(OH)_2CF_3$], –70.79 [d, $^5J_{F,H}$ = 1.8 Hz, 3 F, C(O)CF_3].

2,4-Dibromo-6-(trifluoroacetyl)phenol

Yield: 10 mg (2%); yellow solid; mp 69–73 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.86–7.93 (m, 1 H, 5-H), 8.01 (d, $^4J_{H,H}$ = 2.4 Hz, 1 H, 3-H), 11.5 (br s, 1 H, OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 111.7, 114.0, 115.3 (s, 2-C, 4-C, 6-C), 115.9 (q, $^1J_{C,F}$ = 289.6 Hz, CF_3), 131.9 (q, $^4J_{C,F}$ = 4.2 Hz, 5-C), 144.1 (s, 3-C), 159.9 (s, 1-C), 183.7 [q, $^2J_{C,F}$ = 36.7 Hz, C(O)CF_3].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –70.76 (d, $^5J_{F,H}$ = 1.9 Hz, CF_3).

MS (EI, 70 eV): *m/z* (%) = 346 (67) [M^+], 277 (100) [M – CF_3]$^+$.

HRMS: *m/z* [M]$^+$ calcd for $C_8H_3{}^{79}Br_2F_3O_2$: 345.8452; found: 345.8424; 7.9 ppm, 2.7 mu, $R \approx 10000$.

Ethyl (1*RS*,2*SR*,4*RS*,5*SR*)-1,5-Dibromo-2,4-dihydroxy-9-oxo-2,4-bis(trifluoromethyl)-3-oxabicyclo[3.3.1]nonane-7-carboxylate (6)

Br_2 (1.38 g, 8.6 mmol) was added dropwise to a well-stirred soln of **5f** (1.56 g, 4.3 mmol) in $CHCl_3$ (25 mL). The resulting red soln was stirred for 20 h at r.t., and then heated at reflux for an additional 48 h. The mixture was cooled to r.t. and evaporated to leave a brown oily residue which solidified in several days. Recrystallization of the solid from toluene yielded **6**.

Yield: 1.0 g (43%); white crystals; mp 113–115 °C.

^{1}H NMR (200 MHz, acetone-d_6): δ = 1.23 (t, $^3J_{H,H}$ = 7.1 Hz, 3 H, CH_3), 2.63–2.80 (m, 2 H, 6,8-H), 3.00–3.21 (m, 2 H, 6,8-H), 3.58 (tt, $^3J_{H,H}$ = 13.2, $^3J_{H,H}$ = 4.6 Hz, 1 H, 7-H), 4.14 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, OCH_2), 7.7 (br s, 2 H, 2 × OH).

^{19}F NMR (188 MHz, acetone-d_6): δ = –78.81 (s, CF_3).

MS (EI, 70 eV): *m*/*z* (%) = 518 (1) [M – H_2O]$^+$, 343 (44) [M – H_2O – CF_3CO – Br + H]$^+$, 269 (100) [M – H_2O – CF_3CO – Br – $CO_2C_2H_5$]$^+$, 191 (44) [M – H_2O – CF_3CO – 2 Br – $CO_2C_2H_5$ + H]$^+$, 69 (38) [CF_3^+].

HRMS: *m*/*z* [M – H_2O]$^+$ calcd for $C_{13}H_{10}{}^{79}Br_2F_6O_5$: 517.8799; found: 517.8815; –3.1 ppm, –1.6 mu, *R* ≈ 10000.

4-Hydroxy-3,5-bis(trifluoroacetyl)benzoic Acid (3g)

A soln of **3f** (0.20 g, 0.56 mmol) in concd aq HCl (5 mL) was heated at reflux for 10 h. The mixture was cooled to r.t. and evaporated to dryness. The solid residue was washed with warm $CHCl_3$ (15 mL), and the organic phase was evaporated. Column chromatography of the solid residue (EtOAc) yielded **3g**.

Yield: 60 mg (32%); yellow crystals; melting interval 136–143 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.79 (s, 2,6-H).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.90 (s, CF_3).

MS (EI, 70 eV): *m*/*z* (%) = 330 (8) [M$^+$], 261 (100) [M – CF_3]$^+$, 191 (64) [M – 2 CF_3 – H]$^+$, 69 (4) [CF_3]$^+$.

HRMS: *m*/*z* [M]$^+$ calcd for $C_{11}H_4F_6O_5$: 329.9963; found: 329.9969; –1.9 ppm, –0.6 mu, *R* [a] 10000.

Methyl 4-Hydroxy-3,5-bis(trifluoroacetyl)benzoate (3h)

A 5% aq KOH soln (7 mL) was added dropwise to a stirred soln of **3f** (0.30 g, 0.83 mmol) in MeOH (10 mL) at ca. 18 °C. The resulting soln was left for 48 h at r.t., and then diluted with H_2O (50 mL). The mixture was acidified with 12% aq HCl to pH 1, and extracted with EtOAc (4 × 10 mL). The combined extracts were dried ($MgSO_4$) and concentrated. Column chromatography of the residue ($CHCl_3$) yielded a yellow oil which solidified slowly to afford methyl ester **3h** as a mixture with the corresponding monohydrate (65:35,[28] by NMR).

Yield: 0.15 g (53%); yellow semi-solid.

MS (EI, 70 eV): *m*/*z* (%) = 344 (8) [M$^+$], 313 (20) [M – CH_3O]$^+$, 275 (100) [M – CF_3]$^+$, 205 (40) [M – 2 CF_3 – H]$^+$, 216 (2) [M – CH_3O – CF_3CO]$^+$.

Anal. Calcd for $C_{12}H_6F_6O_5$: C, 41.88; H, 1.76. Found: C, 41.59; H, 1.85.

3h (A ⇆ B)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.98 (s, 3 H, CH_3), 8.74 (s, 2 H, 2,6-H), 12.1 (br s, 1 H, OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.86 (s, CF_3).

Monohydrate Form of 3h

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, CH_3), 4.8, 5.1 (2 br s, 2 × 1 H, 2 × OH), 8.64, 8.73 (2 s, 2 × 1 H, 2-H, 6-H), 12.1 (br s, 1 H, 1-OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –85.73 [s, 3 F, $C(OH)_2CF_3$], –70.80 [s, 3 F, $C(O)CF_3$].

4-Nitro-2,6-bis(trifluoroacetyl)phenol (3i)

Phenol **3b** (1.0 g, 3.5 mmol) was dissolved in concd aq H_2SO_4 (2 mL) at –10 °C. A mixture of 65% HNO_3 (0.25 mL) and concd aq H_2SO_4 (0.5 mL) was added dropwise to this soln at –5 °C. The resulting soln was stirred for 1 h at 0 °C, poured into ice water (100 g), and extracted with Et_2O (4 × 10 mL). The combined extracts were washed with brine (5 mL) and dried (Na_2SO_4). Removal of the solvent gave a solid residue, which was recrystallized (heptane–toluene, 1:1); this furnished **3i** as a mixture with the corresponding monohydrate (67:33,[28] by NMR).

Yield: 0.84 g (73%); pale yellow crystals; melting interval 92–97 °C.

MS (EI, 70 eV): *m*/*z* (%) = 331 (6) [M$^+$], 262 (100) [M – CF_3]$^+$, 216 (32) [M – CF_3 – NO_2]$^+$, 192 (16) [M – 2 CF_3 – H]$^+$, 69 (3) [CF_3^+].

HRMS: *m*/*z* [M]$^+$ calcd for $C_9H_3F_3NO_5$: 261.9963; found: 261.9959; 1.6 ppm, 0.4 mu, *R* ≈ 10000.

3i (A ⇆ B)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.97 (unresolved t, $^5J_{H,F}$ ≈ 0.7 Hz, 2 H, 3,5-H), 12.4 (br s, 1 H, OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –72.98 (s, CF_3).

Monohydrate Form of 3i

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.9 (br s, 2 H, 2 × OH), 8.85–8.90 [m, 1 H, 5(3)-H], 8.95 [s, 1 H, 3(5)-H], 12.4 (br s, 1 H, 1-OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –85.52 [s, 3 F, $C(OH)_2CF_3$], –71.00 [d, $^5J_{F,H}$ = 1.4 Hz, 3 F, $C(O)CF_3$].

Compound 3j by Bromination of 3b (Table 3, entry 4)

To a well-stirred soln of **3b** (2.9 g, 10 mmol) in TFA (5 mL) was added concd aq H_2SO_4 (1.5 mL) at 0 °C. To the resulting brown soln maintained at 0 °C was added NBS (2.7 g, 15 mmol) in several portions within 10 min. The mixture was allowed to warm and stirred for 2 h at r.t., then poured into H_2O (300 mL), and extracted with CH_2Cl_2 (4 × 25 mL). The combined extracts were washed with brine (25 mL) and dried (Na_2SO_4). Removal of the solvent gave an oily residue, which was distilled in vacuo; this gave a yellow liquid (boiling interval 80–110 °C/1 Torr). Column chromatography ($CHCl_3$, then EtOAc) furnished two fractions. The first one (0.5 g of yellow semi-solid after evaporation) consisted of 2,4-dibromo-6-(trifluoroacetyl)phenol, 2,4,6-tribromophenol,[29] and **3j** (1:1:1, by NMR). The second fraction [0.85 g (23%) of yellow semi-solid] was found to be **3j** in mixture with the corresponding mono-hydrate (87:13,[28] by NMR).

Compound 3j by Bromination of 3b (Table 3, entry 5)

Py (50 mg, 0.62 mmol) was added to a well-stirred soln of **3b** (0.16 g, 0.56 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The mixture was allowed to reach r.t., and Br_2 (100 mg, 0.62 mmol) was added. The resulting yellow soln was stirred for 20 h at r.t., poured into H_2O (50 mL), and acidified with 12% aq HCl to pH 1. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layer was dried (Na_2SO_4) and the solvent was evaporated; this left a yellow oil. Column chromatography ($CHCl_3$, then EtOAc) furnished two fractions. The first one (50 mg of yellow solid after evaporation) consisted of 2,4-dibromo-6-(trifluoroacetyl)phenol and 2,4,6-tribromophenol[29] (1:1, by NMR). The second fraction [80 mg (37%) of yellow semi-solid] was found to be **3j** in mixture with the corresponding mono-hydrate (65:35,[28] by NMR).

Compound 3j by Bromination of 3b (Table 3, entry 6)

A soln of **3b** (2.0 g, 7.0 mmol) in anhyd CH_2Cl_2 (30 mL) was cooled to –78 °C, and anhyd py (0.61 g, 7.7 mmol) and Br_2 (1.1 g, 7.7 mmol) were added sequentially. The resulting soln was stirred for 30 min at –78 °C, then for 16 h at r.t. The soln was poured into H_2O (200 mL), the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layer was dried (Na_2SO_4) and the solvent was evaporated to leave a yellow oil. Column chromatography ($CHCl_3$, then EtOAc) furnished two fractions. The first one (0.2 g of yellow oil after evaporation) consisted of starting **3b**, 2,4-dibromo-6-(trifluoroacetyl)phenol, and 2,4,6-tribromophenol[29] (1:1:1, by NMR). The second fraction [1.4 g (57%); yellow semi-solid] was found to be **3j** in mixture with the corresponding mono-hydrate (90:10,[28] by NMR).

2,6-Bis(trifluoroacetyl)-1,4-hydroquinone (3k)

Concd aq HCl (3 mL) was added to a soln of **5k** (3.0 g, 8.6 mmol) in MeOH (40 mL). The resulting soln was heated at reflux for 2 h, cooled to r.t., and stirred for 15 h. The soln was poured into H_2O (250 mL), and extracted with EtOAc (3 × 40 mL). The combined extracts were dried (Na_2SO_4) and evaporated; this left an orange oil, which solidified. The solid was recrystallized (heptane–toluene, 4:1) to give **3k**.

Yield: 0.50 g (19%); orange crystals; mp 140 °C.

^{1}H NMR (200 MHz, acetone-d_6): δ = 7.66 (s, 2 H, 3,5-H), 9.08 (s, 1 H, 4-OH), 11.13 (s, 1 H, 1-OH).

^{13}C NMR (200 MHz, acetone-d_6): δ = 117.1 (q, $^1J_{C,F}$ = 289.6 Hz, CF_3), 120.3 (s, 2,6-C), 125.4 (s, 3,5-C), 150.7 (s, 4-C), 157.6 (s, 1-C), 183.4 [q, $^2J_{C,F}$ = 36.7 Hz, $C(O)CF_3$].

^{19}F NMR (188 MHz, acetone-d_6): δ = –72.92 (s, CF_3).

MS (EI, 70 eV): *m*/*z* (%) = 302 (47) [M$^+$], 233 (100) [M – CF_3]$^+$, 163 (52) [M – 2 CF_3 – H]$^+$, 135 (14) [M – CF_3 – CF_3CO – H]$^+$, 108 (10) [M – 2 CF_3CO]$^+$, 69 (10) [CF_3^+].

HRMS: *m*/*z* [M]$^+$ calcd for $C_{10}H_4F_6O_4$: 302.0014; found: 302.0025; –3.6 ppm, –1.1 mu, $R \approx 10000$.

5,7,16,18-Tetrahydroxy-8,19-bis(trifluoroacetyl)-5,16-bis(trifluoromethyl)-1,4,12,15-tetraoxa[5,5]metacyclophane (8)

Br_2 (0.51 g, 3.2 mmol) was added dropwise to a well-stirred soln of **5k** (0.50 g, 1.45 mmol) in $CHCl_3$ (20 mL). The resulting red soln was stirred in a stoppered flask for 48 h. After opening of the flask (caution: slight internal pressure due to HBr vapors), the precipitate was collected by filtration and air-dried; this yielded product **8**.

Yield: 0.25 g (50%); yellow powder; mp 153 °C.

^{1}H NMR (200 MHz, acetone-d_6): δ = 3.99–4.24 (m, 6 H, 2 CH_2, 2 × CH), 4.54 (ddd, $^2J_{H,H}$ = 10.6, $^3J_{H,H}$ = 8.9, $^3J_{H,H}$ = 1.6 Hz, 2 H, 2 × CH), 7.35 [d, $^3J_{H,H} \approx 2$ Hz, 2 H, 11,22(9,20)-H], 7.66 [d, $^3J_{H,H} \approx 3$ Hz, 2 H, 9,20(11,22)-H], 8.0 (br s, 2 H, 5,16-OH), 10.4 (br s, 2 H, 7,18-OH). The two last signals disappeared after the addition of deuterated acetic acid.

^{1}H NMR (200 MHz, THF-d_8): δ = 3.90–4.10 (m, 6 H, 2 CH_2, 2 × CHH), 4.40–4.51 (m, 2 H, 2 × CHH), 7.25 [d, $^3J_{H,H} \approx 2.4$ Hz, 2 H, 11,22(9,20)-H], 7.61 [d, $^3J_{H,H} \approx 2.9$ Hz, 2 H, 9,20(11,22)-H], 8.2 (br s, 2 H, 5,16-OH), 10.2 (br s, 2 H, 7,18-OH).

^{19}F NMR (188 MHz, acetone-d_6): δ = –85.53 [s, 6 F, 2 × $C(OH)_2CF_3$], –73.87 [s, 6 F, 2 × $C(O)CF_3$].

^{19}F NMR (188 MHz, THF-d_8): δ = –85.86 [s, 6 F, 2 × $C(OH)_2CF_3$], –74.35 [s, 6 F, 2 × $C(O)CF_3$].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –85.80 [s, 6 F, 2 × $C(OH)_2CF_3$], –70.71 [s, 6 F, 2 × $C(O)CF_3$].

^{19}F NMR (188 MHz, CD_3CN): δ = –85.81 (s, 6 F, 2 × $C(OH)_2CF_3$], –73.00 (s, 6 F, 2 × $C(O)CF_3$].

MS (CI, positive): *m*/*z* (%) = 364 (100) [0.5M + NH_4]$^+$, 363 (95) [0.5M + NH_3]$^+$, 346 (30) [0.5M]$^+$.

MS (CI, negative): *m*/*z* (%) = 346 (100) [0.5M]$^-$, 326 (98) [0.5M – HF]$^-$.

MS (EI, 70 eV): *m*/*z* (%) = 346 (44) [0.5M]$^+$, 302 (10) [0.5M – CH_2CH_2O]$^+$, 277 (20) [0.5M – CF_3]$^+$, 233 (100) [0.5M – CH_2CH_2O – CF_3]$^+$, 163 (12) [0.5M – CH_2CH_2O – 2 CF_3 – H]$^+$, 45 (18) [C_2H_5O]$^+$.

HRMS: *m*/*z* [0.5M]$^+$ calcd for $C_{12}H_8F_6O_5$: 346.0276; found: 346.0279; –0.9 ppm, –0.3 mu, $R \approx 10000$.

Anal. Calcd for $C_{24}H_{16}F_{12}O_{10}$: C, 41.64; H, 2.33; F, 32.9. Found: C, 41.56; H, 2.40; F, 32.7

2,5-Bis(trifluoroacetyl)cyclohexane-1,4-dione (9a)

CF_3CO_2Et (10.5 g, 74 mmol) was added to an ice-cooled suspension of NaOMe (4.4 g, 80 mmol) in anhyd Et_2O (100 mL) under stirring, after which cyclohexane-1,4-dione (3.9 g, 35 mmol) was added in several portions. The mixture was stirred for 24 h at r.t. After treatment with 10% aq H_2SO_4 (80 mL), the mixture was stirred for 10 min and extracted with Et_2O (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The solid residue was recrystallized (heptane–toluene, 2:1).

Yield: 6.1 g (56%); orange crystals; melting interval 115–120 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.60 (s, 4 H, 2,5-H), 14.57 (s, 2 H, 2 × OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –74.61 (t, $^5J_{F,H} \approx 0.9$ Hz, CF_3).

MS (EI, 70 eV): *m*/*z* (%) = 304 (100) [M$^+$], 235 (40) [M – CF_3]$^+$, 207 (34) [M – CF_3CO]$^+$, 97 [26] [CF_3CO^+], 69 (48) [CF_3^+].

HRMS: *m*/*z* [M]$^+$ calcd for $C_{10}H_6F_6O_4$: 304.0170; found: 304.0153; 5.7 ppm, 1.7 mu, $R \approx 10000$.

2,5-Bis(2,2,3,3-tetrafluoropropionyl)cyclohexane-1,4-dione (9b)

Method A: $HCF_2CF_2CO_2Me$ (3.0 g, 18.5 mmol) was added to an ice-cooled suspension of NaOMe (1.0 g, 18.5 mmol) in anhyd Et_2O (30 mL) under stirring, after which cyclohexane-1,4-dione (1.0 g, 8.9 mmol) was added in several portions. The mixture was stirred for 24 h at r.t. After treatment with 10% aq H_2SO_4 (20 mL), the mixture was stirred for 10 min and then extracted with Et_2O (4 × 15 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The oily residue was dissolved in $CHCl_3$ and filtered through a bed of silica gel, and the filter pad was washed with $CHCl_3$. The filtrate was evaporated, and the solid residue was recrystallized from heptane.

Yield: 100 mg (3%); yellow needles; mp 83–85 °C.

Method B: A soln of cyclohexane-1,4-dione (1.0 g, 8.9 mol) in anhyd THF (10 mL) was added dropwise to a mixture of a 1.8 M soln of (commercially obtained) LDA in heptane–THF–ethylbenzene (10 mL) and THF (20 mL) maintained at –78 °C. After the mixture had stirred for 40 min, $HCF_2CF_2CO_2Me$ (2.9 g, 18.0 mmol) was added via cannula. The reaction mixture was warmed to r.t. and stirred for 12 h. After treatment with 10% aq H_2SO_4 (20 mL), the mixture was stirred for 10 min and then extracted with Et_2O (4 × 15 mL). The combined extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography ($CHCl_3$).

Yield: 0.60 g (18%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.68 (t, $^5J_{H,F}$ = 1.5 Hz, 4 H, 2,5-H), 6.18 (tt, $^2J_{H,F}$ = 52.6, $^3J_{H,F}$ = 5.3 Hz, 2 H, 2 × CF_2H), 15.04 (s, 2 H, 2 × OH).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –139.41 (dt, $^2J_{F,H}$ = 52.6, $^3J_{F,F}$ = 7.2 Hz, 4 F, 2 × CF_2CF_2H), –122.01 (m, 4 F, 2 × CF_2CF_2H).

MS (EI, 70 eV): *m/z* (%) = 368 (100) [M^+], 267 (100) [M – $CF_2CF_2H]^+$, 239 (68) [M – $HCF_2CF_2CO]^+$, 110 (30) [M – 2 $HCF_2CF_2CO]^+$, 101 (36) [$CF_2CF_2H^+$], 51 (16) [$CF_2H]^+$.

HRMS: *m/z* [M]$^+$ calcd for $C_{12}H_8F_8O_4$: 368.0295; found: 368.0295; –0.1 ppm, 0.0 mu, $R \approx 10000$.

2,5-Bis(fluoroacyl)-1,4-hydroquinones 11; General Procedure

Br_2 (0.54 g, 2.1 mmol) was added dropwise to a well-stirred soln of the appropriate **9** (2.1 mmol) in $CHCl_3$ (5 mL) at r.t. The resulting red soln was stirred in a stoppered flask for 10 h. After opening of the flask (caution: slight internal pressure due to HBr vapors), the volatile materials were evaporated, and the residue was recrystallized from heptane.

2,5-Bis(trifluoroacetyl)-1,4-hydroquinone (11a)

Yield: 88%; orange crystals; mp 131–134 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.59 (q, $^5J_{H,F}$ = 2.0 Hz, 2 H, 3,5-H), 10.04 (s, 2 H, 2 × OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 115.8 (q, $^1J_{C,F}$ = 289.8 Hz, CF_3), 120.1 (s, 2,5-C), 120.1 (q, $^4J_{C,F}$ = 3.8 Hz, 3,6-C), 154.6 (s, 1,4-C), 184.4 [q, $^2J_{C,F}$ = 36.7 Hz, $C(O)CF_3$].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –71.41 (d, $^5J_{F,H}$ = 1.9 Hz, CF_3).

MS (EI, 70 eV): *m/z* (%) = 302 (56) [M^+], 233 (100) [M – $CF_3]^+$, 205 (2) [M – $CF_3CO]^+$, 69 (12) [CF_3^+].

HRMS: *m/z* [M]$^+$ calcd for $C_{10}H_4F_6O_4$: 302.0014; found: 302.0008; 2.1 ppm, 0.6 mu, $R \approx 10000$.

2,5-Bis(2,2,3,3-tetrafluoropropionyl)-1,4-hydroquinone (11b)

Yield: 86%; orange crystals; mp 116–117 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.27 (tt, $^2J_{H,F}$ = 52.3, $^3J_{H,F}$ = 5.1 Hz, 2 H, 2 × CF_2H), 7.73 (t, $^5J_{H,F}$ = 2.0 Hz, 2 H, 3,5-H), 10.1 (br s, 2 H, 2 × OH).

^{13}C NMR (200 MHz, $CDCl_3$): δ = 108.4 (tt, $^1J_{C,F}$ = 252.2, $^2J_{C,F}$ = 31.6 Hz, CF_2H), 110.1 (tt, $^1J_{C,F}$ = 264.9, $^2J_{C,F}$ = 27.3 Hz, CF_2CO), 120.4 (t, $^4J_{C,F}$ = 6.8 Hz, 3,6-C), 121.3 (t, $^3J_{C,F}$ = 2.5 Hz, 2,5-C), 154.5 (s, 1,4-C), 190.2 [t, $^2J_{C,F}$ = 28.5 Hz, $C(O)CF_2$].

^{19}F NMR (188 MHz, $CDCl_3$): δ = –138.38 (dt, $^2J_{F,H}$ = 52.5, $^3J_{F,F}$ = 6.4 Hz, 4 F, 2 × CF_2H), –117.09 (m, $^5J_{F,H}$ = 2.0 Hz, 4 F, 2 × CF_2CO).

MS (EI, 70 eV): *m/z* (%) = 366 (64) [M^+], 265 (100) [M – $CF_2CF_2H]^+$.

HRMS: *m/z* [M]$^+$ calcd for $C_{12}H_6F_8O_4$: 366.0138; found: 366.0138; 0.2 ppm, 0.1 mu, $R \approx 10000$.

4-Methyl-2,6-bis(trifluoroacetyl)anisole (2)

A 1.6 M soln of BuLi in hexane (73 mL, 117 mmol) was added dropwise to a soln of **1** (16.0 g, 57 mmol) in anhyd THF (100 mL) maintained at –78 °C. After the mixture had stirred for 1 h at this temperature, CF_3CO_2Et (17.0 g, 120 mmol) was added dropwise. The reaction mixture was allowed to reach r.t. and stirred for 1 h. After successive treatment of the mixture with 10% aq NH_4Cl (30 mL) and 10% aq HCl (100 mL), the aqueous layer was saturated with NaCl and the organic layer was separated. After extraction with Et_2O (4 × 30 mL), the combined organic phases were washed successively with brine (30 mL) and H_2O (30 mL), dried (Na_2SO_4), and concentrated. Distillation of the residue gave the product.

Yield: 9.8 g (55%); yellow liquid; bp 52 °C/1 Torr.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, $ArCH_3$), 3.69 (s, 3 H, OCH_3), 7.67 (s, 2 H, 3,5-H).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –77.93 (s, CF_3).

MS (EI, 70 eV): *m/z* (%) = 314 (28) [M^+], 245 (100) [M – $CF_3]^+$, 69 (4) [$CF_3]^+$.

Anal. Calcd for $C_{12}H_8F_6O_3$: C, 45.88; H, 2.57; F, 36.3. Found: C, 45.68; H, 2.61; F, 35.8.

Deprotection of 2

A soln of **2** (18.0 g, 57 mmol) in anhyd CH_2Cl_2 (10 mL) was placed in a thick-walled glass ampule equipped with a Teflon tap, and then BCl_3 (10.0 g, 86 mmol) was condensed into the evacuated ampule at liquid N_2 temperature. The mixture was gradually allowed to warm and stirred for 1 h at r.t. After the volatile materials had been removed in vacuo, the content of the ampule was carefully treated with an ice–water mixture (20 mL). The resulting mixture was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). The organic layer was separated, washed with H_2O (4 × 50 mL), dried (Na_2SO_4), and concentrated. Recrystallization of the residue from hexane at –50 °C gave **3a**.

Yield: 12.0 g (70%).

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