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Synthesis and Nucleophilic Substitution Reactions of Mono α-Fluoro Ethers

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Mono α-fluoro ethers have been prepared by cleavage of α-alkoxy sulfoxides with diethylaminosulfur trifluoride (DAST) and by an exchange reaction of the corresponding α-chloro ether with tetrabutylammonium fluoride (TBAF). The reactivity of different α-fluoro ethers in some nucleophilic substitution reactions has been investigated.

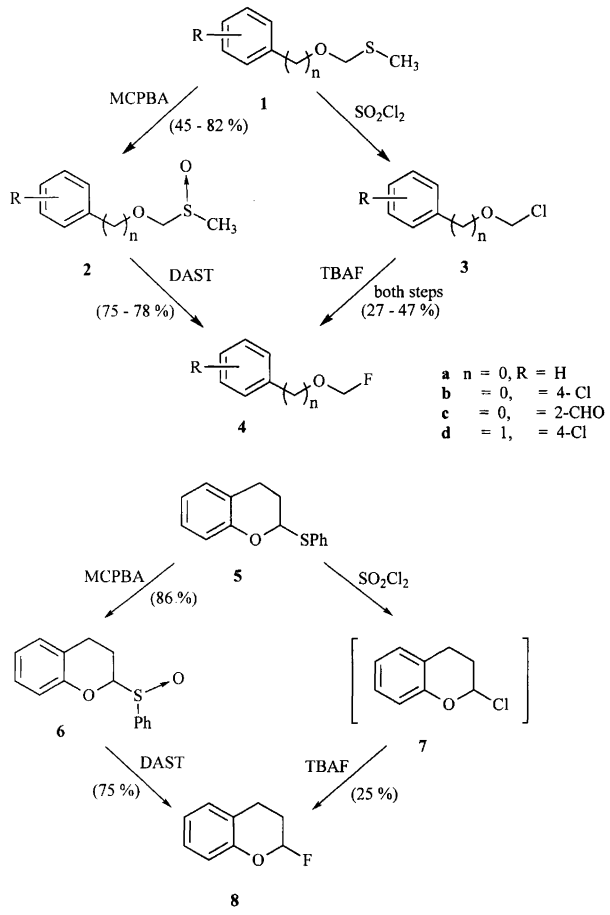
Simple alkyl fluorides have usually very low reactivity in nucleophilic substitution reactions, because the fluoride ion is a poor leaving group.[1] The ability of a group to function as as leaving group is, however, dependent on the structure of the substrate.[2] The aim of this study was to see whether simple α-fluoro ethers would undergo nucleophilic substitution reactions and how the structure of the α-fluoro ether influences the reactivity.

In order to have ready access to α-fluoro ethers, new synthetic strategies had to be developed.

Syntheses of α-fluoro ethers. Glycosyl fluorides have been made in a number of ways,[3] but the syntheses of simple aliphatic α-fluoro ethers are much less well developed. Traditionally they have been prepared by halogen exchange of α-chloro ethers with mercury(II) fluoride.[4] More recently XeF_2 has been used to make α-fluoro ethers, in a rearrangement reaction of benzylic alcohols,[5] in a decarboxylation of α-aryloxyacetic acids[6] and in a cleavage reaction of *O,S*-acetals.[7]

We have previously demonstrated that α-chloro and α-bromo ethers can be prepared from α-alkoxy sulfoxides by treatment with acetyl chloride or trimethylsilyl bromide, respectively.[8] In this report we show that α-fluoro ethers can also be made from α-alkoxy sulfoxides. The sulfinyl group is replaced with fluorine using diethylaminosulfur trifluoride (DAST). The α-alkoxy group in the sulfoxide is very important for this reaction to succeed, because without an α-alkoxy group or anything else that can stabilize a carbocation, sulfoxides give α-fluoro sulfides in the reaction with DAST.[9]

The α-fluoro ethers **4** were prepared by treatment of the sulfoxides **2** with 1.5 equivalents of DAST in dichloromethane at ambient temperature (Scheme 1). The isolated yields were between 75 and 80%. A phenylsulfinyl group can also be split off to give α-fluoro ethers in good yield, as demonstrated in the reaction of phenyl sulfoxide **6** with DAST (Scheme 1).



Scheme 1.

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The α-fluoro ethers **4** and **8** were also prepared by an exchange reaction of the α-chloro ethers **3**/**7** and tetrabutylammonium fluoride (TBAF). The yields in this reaction were, however, lower than in the cleavage reaction with DAST. In the case of **7** some elimination also took place to give the dihydro derivative **16**.

One convenient way to prepare α-fluoro ethers is to replace the OH-group in hemiacetals with fluorine. This can be done using DAST.[9] The method of course requires that the hemiacetal be fairly stable under the reaction conditions. This is the case for 2-hydroxy-3,4-dihydro-2*H*-1-benzopyran, which upon treatment with DAST for 5 min gave 3,4-dihydro-2-fluoro-2*H*-1-benzopyran (**8**) in 81% yield.

Reactions of α-fluoro ethers in nucleophilic substitution reactions. As nucleophiles in substitution reactions with the α-fluoro ethers, both heteroatom and carbon nucleophiles were investigated.

Glycosyl fluorides have shown good reactivity with alcohols in the presence of tin dichloride and silver perchlorate.[10] We tried the same system in the reaction of the α-fluoro ethers **4b**, **4d** and **8** with cyclohexanol (Scheme 2). In the reaction of **4b** only the hydrolysis product 4-chlorophenol was isolated. With the α-fluoro ether **4d** the substitution product **9a** was isolated in 63% yield (entry 2, Scheme 2) together with the acetal **10** (10%). The α-fluoro ether **8** also reacted with cyclohexanol under the conditions mentioned above, to give the substitution product **9b** in 56% yield and the hydrolysis product **11** (20%).

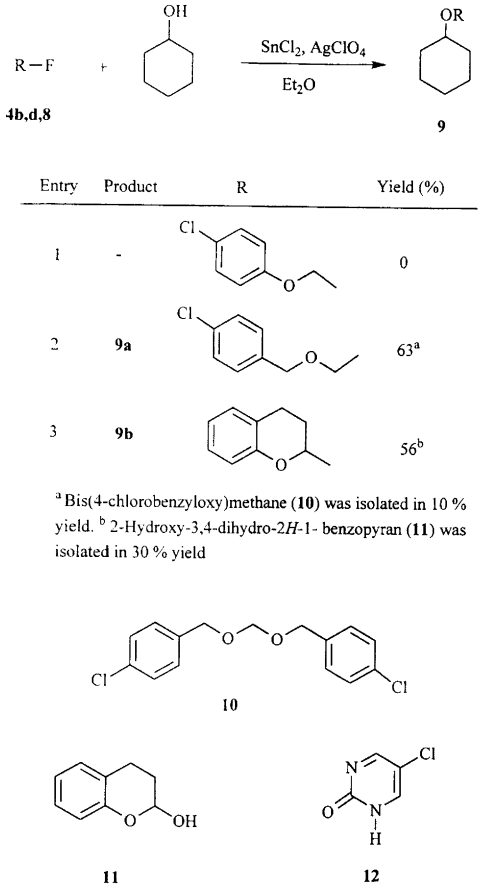
5-Chloro-2-pyrimidinone (**12**) was chosen as an example of an amide nucleophile, because we have earlier studied the reaction of α-chloro ethers with this compound.[11] The pyrimidinone did not react with the α-fluoro ether **4d** under basic conditions (triethylamine, dichloromethane). This is in sharp contrast with the corresponding α-chloro ether which reacts readily with the pyrimidinone under these conditions.[11] Lewis acid conditions were also tried but the only isolated product was the acetal **10**.

As carbon nucleophiles compounds with different nucelophilicities were selected: 1-phenyl-1-trimethylsilyloxyethene, allyltrimethylsilane, butyllithium, butylmagnesium bromide, vinylmagnesium bromide and butylzinc bromide.

The α-fluoro ethers **4a** and **4d** were reacted with 1-phenyl-1-trimethylsilyloxyethene in the presence of tetrabutylammonium fluoride (TBAF). No reaction occured (Scheme 3).

In the presence of a stoichiometric amount of $ZnBr_2$, allyltrimethylsilane reacted with the α-fluoro ether **4d** to give the homoallylic ether **13** in 59% yield (Scheme 3).

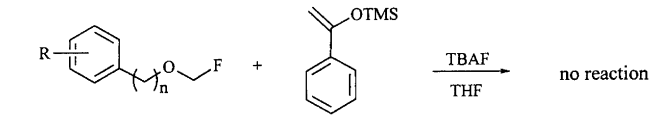
A catalytic amount of $ZnBr_2$ gave a reduced yield. In this reaction an exchange reaction between the α-fluoro ether and $ZnBr_2$ may take place so the reacting species may be the corresponding α-bromo ether to compound **4d**.



[a] Bis(4-chlorobenzyloxy)methane (**10**) was isolated in 10 % yield. [b] 2-Hydroxy-3,4-dihydro-2*H*-1- benzopyran (**11**) was isolated in 30 % yield

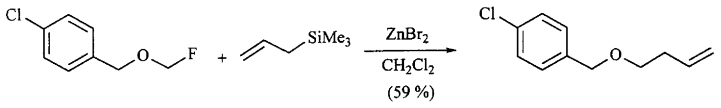
Scheme 2.

It is well known that α-chloro and α-bromo ethers can react with organometallic compounds to give substitution products.[12] For instance, the reaction between a Grignard reagent and an α-bromo ether is the key step in the Boord olefination reaction.[13] Other reactions may, however, occur. For example when α-chloro ethers are treated with an organolithium compound hydrogen–lithium exchange may take place to give carbenoid α-lithio-α-chloro ethers. α-Elimination of lithium chloride from these compounds gives the corresponding alkoxy carbenes.[14] In order to study whether α-fluoro ethers behave differently from α-chloro ethers in reactions with organometallic compounds, **4a** was treated with butyllithium at −20 °C in the presence of cyclohexene. Only substitution was observed and pentyloxybenzene (**14a**) was isolated in 85% yield (entry 1, Scheme 4). When the corresponding α-chloro ether was reacted in the same way, only 14% of the isolated product was the substitution product **14a**, while 38% was the carbene addition product 7-phenoxynorcarane.[14a] The α-fluoro ether **4d** behaved similarly to **4a** in this reaction (entry 5, Scheme 4). The α-fluoro ethers **4a** and **4d** also reacted well in substitution reactions with butylmagnesium bromide (entries 2 and 6, Scheme 4). Vinylmagnesium bromide gave a somewhat lower yield (entries 4 and 8, Scheme 4). Softer nucleophiles such as organozinc compounds seem to be less



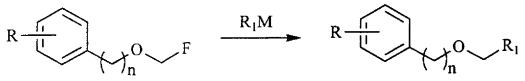
4a,d

R = H, 4-Cl; n = 0, 1



4d **13**

Scheme 3.



4a,d **14**

Entry	Product	n	R	R_1M	Yield (%)
1	**14a**	0	H	BuLi	85
2	**14a**	0	H	BuMgBr	77
3	**14a**	0	H	BuZnBr	10
4	**14b**	0	H	vinylMgBr	52
5	**14c**	1	4-Cl	BuLi	66
6	**14c**	1	4-Cl	BuMgBr	67
7	**14c**	1	4-Cl	BuZnBr	20
8	**14d**	1	4-Cl	vinylMgBr	64

Scheme 4.

useful in this reaction (entries 3 and 7, Scheme 4; entry 3, Scheme 5).

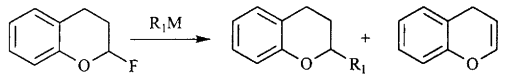
In the case of the secondary α-fluoro ether **8** elimination was the preferred reaction pathway with butyllithium (entry 1, Scheme 5). Variation in the reaction temperature did not reduce the amount of elimination product to any great extent.

Grignard reagents are weaker bases than organolithium compounds[15] and should cause less elimination to occur. Thus the reaction of the α-fluoro ether **8** with butylmagnesium bromide gave the substitution product as the main product while the elimination product was formed only in small amounts (entry 2, Scheme 5). In the reaction with vinylmagnesium bromide, however, elimination was again a significant reaction (entry 4, Scheme 5).

Conclusions

α-Fluoro ethers can be made by an exchange reaction of α-chloro ethers with fluoride ions or by a cleavage reaction of α-alkoxy sulfoxides with DAST. The latter method gives overall a better yield of α-fluoro ethers starting from the corresponding *O,S*-acetal.

The reactivity of the α-fluoro ethers in substitution reactions seems to depend very much upon their structure. Anything pulling electrons away from the oxygen reduces the reactivity, whereas electron-donating groups have the opposite effect.



8 **15** **16**

Entry	Product	R_1M	Yield (%)	Yield (%)
1	**15a**	BuLi	16	50
2	**15a**	BuMgBr	60	5
3	**15a**	BuZnBr	<10	-
4	**15b**	vinylMgBr	42	30

Scheme 5.

In order to optimise yields in substitution reactions with α-fluoro ethers, good and hard nucleophiles give the best results. In contrast with α-chloro ethers, substitution reactions with such nucleophiles can be performed without α-elimination. This is a feature which might be useful in synthetic organic chemistry.

Experimental

The NMR spectra were recorded in $CDCl_3$ at 200 MHz (^1H), at 50 MHz (^{13}C) and at 188 MHz (^{19}F). The chemical shifts are given in ppm downfield from tetramethylsilane. The mass spectra, under electron impact conditions, were recorded at 70 eV ionizing energy. Methane was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.). Compounds reported in the literature are: **1a**,[16] **1b**,[17] **1d**,[18] **2a**,[19] **3a**,[20] **3b**,[20] **3d**,[19] **5**.[21]

2-(Methylthio)methoxybenzaldehyde **1c**. Sodium hydride (1.80 g, 60.0 mmol, 80% in paraffin) and sodium iodide (8.24 g, 55.0 mmol) were added to a solution of 2-hydroxybenzaldehyde (6.00 g, 49.0 mmol) in DMF (100 ml) at 0 °C under N_2. After 10 min chloromethyl methyl sulfide (6.38 mmol, 75.6 mmol) was added and the mixture stirred for 12 h during which time it reached ambient temperature. The mixture was poured onto ice,

extracted into diethyl ether, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using 10% ethyl acetate in hexane for elution. Yield: 2.30 g (25%). Oil. ^1H NMR: δ 2.28 (CH_3, s), 5.29 (CH_2, s), 7.03–7.26 (Ar, 2 H, m), 7.52–7.61 (Ar, 1 H, m), 7.84–7.89 (Ar, 1 H, m), 10.50 (CHO, s). ^{13}C NMR: δ 14.9 (CH_3), 73.2 (CH_2), 114.3 (CH), 121.8 (CH), 126.1 (C), 128.7 (CH), 135.5 (CH), 159.4 (C), 189.5 (CHO). High resolution MS: Found 182.0410. Calc. for $C_9H_{10}O_2S$: 182.0401. MS (EI): 182 (M^+, 7), 149 (24), 135 (35), 121 (32), 77 (26), 61 (92), 44 (100).

General procedure for the preparation of aryl and benzyl methylsulfinylmethyl ethers **2**. *m*-Chloroperbenzoic acid (10.5 mmol) was added to a solution of the aryl or benzyl methylthiomethyl ether **2** (10.0 mmol) in dichloromethane (50 ml) at 0 °C. The mixture was stirred for 10 min, shaken with saturated sodium bisulfite solution and then with sodium bicarbonate solution before the dried ($MgSO_4$) solution was evaporated to leave the crude product, which was further purified as described for each compound.

1-Chloro-4-(methylsulfinylmethoxy) benzene **2b**. The crude product was recrystallized from hexane. Yield: 64%. ^1H NMR: δ 2.69 (CH_3, s), 4.88 (CH_2, H_A, J_{gem} 10.3 Hz), 4.98 (CH_2, H_B, d, J_{gem} 10.3 Hz), 6.99–7.33 (Ar, 4 H, m). ^{13}C NMR: δ 35.6 (CH_3), 84.5 (CH_2), 117.0 (CH), 128.1 (C), 129.8 (CH), 156.1 (C). High resolution MS: Found 204.0018. Calc. for $C_8H_9ClO_2S$: 204.0012. MS (EI): 206/204 (M^+, 2/6), 143/141 (32/100), 111 (80), 75 (28).

1-Chloro-4-(methylsulfinylmethoxymethyl)benzene **2d**. The crude product was purified by flash chromatography on silica gel using methanol–ethyl acetate 1 : 10 for elution. Yield: 45%. ^1H NMR: δ 2.63 (CH_3, s), 4.47 (CH_2, H_A, d, J_{gem} 10.7 Hz), 4.56 (CH_2, H_B, d, J_{gem} 10.7 Hz), 4.82 (CH_2, H_A, d, J_{gem} 11.9 Hz), 4.91 (CH_2, H_B, d, J_{gem} 11.9 Hz), 7.2–7.4, Ar, m). ^{13}C NMR: δ 35.1 ($SOCH_3$), 74.6 (OCH_2), 86.6 ($ArCH_2O$), 128.9 (CH), 129.4 (CH), 134.8 (C), 134.3 (C). MS (CI): $M-93$ (100).

2-Chloromethoxybenzaldehyde **3c**. Sulfuryl chloride (0.24 ml, 3.0 mmol) in dichloromethane (1 ml) was added to a solution of **1c** (0.50 g, 2.75 mmol) in dichloromethane (5 ml) at 0 °C. The mixture was stirred for 10 min and evaporated. The crude product was used in the preparation of **4c**. Yield: 0.45 g (96%). ^1H NMR: δ 5.98 (CH_2, s), 7.16–7.30 (Ar, 2 H, m), 7.58–7.67 (Ar, 1 H, m), 7.87–7.91 (Ar, 1 H, m), 10.43 (CHO, s). ^{13}C NMR: δ 76.6 (CH_2), 114.5 (CH), 123.5 (CH), 126.3 (C), 128.9 (CH), 135.8 (CH), 157.6 (C), 189.0 (CHO). High resolution MS: Found 170.0128. Calc. for $C_8H_7ClO_2$: 170.0135. MS (EI): 172/170 (M^+, 5/16), 135 (65), 121 (30), 105 (33), 77 (37), 65 (22), 51 (21), 28 (100).

Fluoromethoxybenzene **4a**.[17] *Method A*. DAST (0.16 ml, 1.2 mmol) was added to a solution of **2a** (130 mg, 0.76 mmol) in dichloromethane (5ml) at 0 °C under N_2. The mixture was stirred at ambient temperature for 36 h before it was poured into ice–water (5 ml) and extracted with dichloromethane (2 × 5ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane for elution. Yield: 70 mg (75%).

Method B. Sulfuryl chloride (4.64 g, 34.4 mmol) in dichloromethane (50 ml) was added to a solution of **1a** (5.30 g, 34.4 mmol) in dichloromethane (50 ml). The mixture was stirred for 10 min, evaporated and redissolved in dichloromethane (50 ml) before TBAF (100 ml, 60 mmol, 0.6 M in THF) was added at 0 °C under N_2. The mixture was stirred for 48 h, poured into ice–water and extracted with diethyl ether, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane for elution. Yield: 1.15 g (27%).

1-Chloro-4-fluoromethoxybenzene **4b**.[17] DAST (0.27 ml, 2.0 mmol) was added to a solution of **2b** (210 mg, 1.0 mmol) in dichloromethane (5 ml) at 0 °C under N_2. The mixture was stirred at ambient temperature for 30 h before it was poured into ice–water (5 ml) and extracted with dichloromethane (2 × 5ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane for elution. Yield: 120 mg (75%).

2-Fluoromethoxybenzaldehyde **4c**. TBAF (5.0 ml, 5.0 mmol, 1.0 M in dichloromethane) was added to a solution of **3c** (400 mg, 2.3 mmol) in dichloromethane (4 ml) at 0 °C under N_2. The mixture was stirred for 20 h at ambient temperature, poured into ice–water, extracted with diethyl ether, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using dichloromethane–hexane 10 : 15 for elution. Yield: 170 mg (47%). ^1H NMR: δ 5.84 (CH_2, d, J_{H-F} 53.7 Hz), 7.16–7.25 (Ar, 2 H, m), 7.56–7.64 (Ar, 1 H, m), 7.85–7.90 (Ar, 1 H, m), 10.47 (CHO, s). ^{13}C NMR: δ 100.7 (CH_2F, J_{C-F} 221 Hz), 115.8 (d, $CHCOCH_2F$, J_{C-F} 1.6 Hz), 124.1 (CH), 126.3 (CCHO), 129.0 (CH), 136.4 (CH), 159.0 ($COCH_2F$, J_{C-F} 2.9 Hz), 189.5 (CHO). ^{19}F NMR: δ −150.22 (t, J_{F-H} 53.7 Hz). High resolution MS: Found 154.0435. Calc. for $C_8H_7FO_2$: 154.0430. MS (EI): 154 (M^+, 68), 136 (14), 125 (23), 121 (29), 105 (100), 77 (51), 44 (60).

1-Chloro-4-(fluoromethoxymethyl) benzene **4d**. *Method A*. DAST (1.04 ml, 7.5 mmol) was added to a solution of **2d** (1.09 g, 5.0 mmol) in dichloromethane (20 ml) at 0 °C under N_2. The mixture was stirred at ambient temperature for 48 h before it was poured into ice–water (5 ml) and extracted with pentane (3 × 20 ml), dried ($MgSO_4$) and evaporated. Yield: 0.68 g (78%).

Method B. Sulfuryl chloride (0.41 g, 5.0 mmol) in

dichloromethane (5 ml) was added to a solution of **3d** (1.51 g, 5.0 mmol) in dichloromethane (5 ml). The mixture was stirred for 10 min, evporated and redissolved in dichloromethane (10 ml) before TBAF (12 ml, 7.2 mmol, 0.6 M in THF) was added under N_2. The mixture was stirred for 1 h and evaporated before it was extracted with pentane (5 × 20 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by distillation. Yield: 0.31 g (36%). B.p 35 °C, 0.25 mmHg) ^{1}H NMR: δ 4.74 (CH_2O, s), 5.33 (CH_2F, d J_{H-F} 56.0 Hz), 7.24–7.37 (Ar, 4 H, m). ^{13}C NMR: δ 71.0 (CH_2O), 102.3 (CH_2F, d, J_{C-F} 214.4), 128.7 (CH), 129.3 (CH), 134.0 (C), 135.0 (C). ^{19}F NMR: δ −152.8 (t, J_{F-H} 56.0 Hz). MS (EI): 176/174 (M^+, 5/12), 127/125 (33/100), 89 (22).

*3,4-Dihydro-2-phenylsufinyl-2*H*-1-benzopyran* **6**. Compound **6** was prepared as described for **2** above from MCPBA (1.58 g, 6.4 mmol, 70%) and **5** (1.54 g, 6.4 mmol). Yield: 1.41 g (86%). Diastereomeric ratio 1:5 (^{1}H NMR).The major isomer was purified by flash chromatography (elution: dichloromethane) and characterized. ^{1}H NMR: δ 2.1–2.4 (CH_2, 1 H, m), 2.6–2.8 (CH_2, m), 3.0–3.3 (CH_2, 1 H, m), 4.7–4.8 (CH, m), 6.7–7.2 (Ar, 4 H, m) 7.4–7.8 (Ar, 5 H, m). ^{13}C NMR: δ 20.4 ($ArCH_2CH_2$), 21.1 ($ArCH_2$), 93.3 (CHS), 116.7 (CH), 121.8 (CH), 125.0 (CH), 127.8 (CH), 129.0 (CH), 129.8 (CH), 131.4 (CH), 131.7 (C), 141.5 (C), 152.1 (C). MS (EI) 258 (M^+, 0.3), 133.3 (100), 105 (60), 77 (41), 51 (22). IR (film): 1175 cm^{-1}, S=O.

*3,4-Dihydro-2-fluoro-2*H*-1-benzopyran* **8**. *Method A.* DAST (0.69 ml, 5.3 mmol) was added to a solution of **6** (0.91 g, 3.5 mmol) in dichloromethane (6 ml) at 0 °C under N_2. The mixture was stirred at ambient temperature for 36 h before it was evaporated and extracted with cold (0 °C) pentane (5 × 10 ml). The pentane solution was washed with ice–water (20 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using dichloromethane–hexane 1:9 for elution. Yield: 0.37 g (70%).

Method B. Sulfuryl chloride (0.33 ml, 4.1 mmol) was added to a solution of **5** (1.00 g, 4.1 mmol) in dichloromethane (20 ml) at 0 °C under N_2. The mixture was stirred for 10 min before cyclohexene (0.51 ml, 5.0 mmol) in dichloromethane (5 ml) was added dropwise. After 10 min the mixture was evaporated and redissolved in dichloromethane (5 ml) before TBAF (12 ml, 7.2 mmol, 0.6 M in THF) was added dropwise at 0 °C under N_2. The mixture was stirred for 20 min and evaporated before the residue was cooled to 0 °C and extracted with cold (0 °C) pentane (5 × 10 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using dichloromethane–hexane 1:9 for elution. Yield: 0.16 g (25%).

Method C. DAST (0.66 ml 5.0 mmol) was added to a solution of 2-hydroxy-3,4-dihydro-2*H*-1-benzopyran (0.75 g, 5.0 mmol) in dichloromethane (10 ml) at 0 °C under N_2. The mixture was stirred for 5 min at ambient temperature before the solvent was evaporated off and the residue extracted into cold (0 °C) pentane (5 × 10 ml) The pentane solution was washed with ice–water (20 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using dichloromethane–hexane 1:9 for elution. Yield: 0.62 g (81%).

^{1}H NMR: δ 1.70–2.20 (CH_2, 1 H, m), 2.20–2.40 (CH_2, 1 H, m), 2.52–2,75 (CH_2, H_{ax} m, J_{gem} 16.3 Hz), 2.80–3.05 (CH_2, H_{eq}, m, J_{gem} 16.3 Hz), 6.05 (CH, d, J_{H-F} 56 Hz), 6.75–7.25 (Ar, 4 H, m). ^{13}C NMR: δ 18.5 (CH_2, d, J_{C-F} 4.4 Hz), 25.6 (CH_2, d, J_{C-F} 41.1 Hz), 104.6 (CH, d, J_{C-F} 219.33), 116.9 (CH), 121.8 (C), 121.9 (CH), 127.7 (CH), 129.2 (CH), 150.2 (C). ^{19}F NMR: δ −128.65 (CHF, dd J_{F-H} 56 Hz, J_{F-H} 56 Hz. High resolution MS: Found 152.0640. Calc. for C_9H_9FO: 152.0637. MS (EI): 152 (M^+, 45), 132 (45), 131 (100), 106 (16), 78 (35), 43 (75).

4-Chlorobenzyloxy(cyclohexyloxy)methane **9a**. The α-fluoro ether **4d** (0.17 g, 1.0 mmol) was added to a solution of $AlClO_4$ (0.23 g, 1.0 mmol), $SnCl_2$ (0.19 g, 1.0 mmol) and cyclohexanol (0.11 g, 1,1 mmol) in dry diethyl ether (4 ml) at −30 °C under N_2. The mixture was slowly allowed to reach ambient temperature and stirred for 12 h before being filtered. The filtrate was washed with a saturated solution of $NaHCO_3$ (2 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography using dichloromethane–hexane 1:4 for elution. Yield: 0.16 g (63%). Oil. ^{1}H NMR: δ 1.20–1.60 (CH_2, 6 H, m), 1.70–2.00 (CH_2, 4 H, m), 3.55–3.65 (OCH, m) 4.58 ($ArCH_2O$, s), 4.80 (OCH_2O, s), 7.24–7.35 (Ar, 4 H, m). ^{13}C NMR: δ 24.2 (CH_2), 25.6 (CH_2), 32.7 (CH_2), 68.4 ($ArCH_2O$), 75.4 (CH), 92.6 (OCH_2O), 128.5 (CH), 129.1 (CH), 133.3 (C), 136.6 (C). MS (EI): 256/254, (M^+, 0.1/0.3), 171 (2), 156/154 (6/18), 127/125 (32/100), 83 (14), 55 (15), 29 (6).

*3,4-Dihydro-2-(cyclohexyloxy)-2*H*-1-benzopyran* **9b**. The α-fluoro ether **8** (0.30 g, 2.0 mmol) in diethyl ether (2 ml) was added dropwise to a solution of $AgClO_4$ monohydrate (0.45 g, 2.0 mmol) $SnCl_2$ (0.38 g, 2.0 mmol), cyclohexanol (0.20 g, 2.0 mmol) and 4 Å molecular sieves in diethyl ether (5 ml) at −30 °C under N_2. The mixture was warmed to ambient temperature, stirred for 30 min and filtered. The solid material was washed with diethyl ether and combined diethyl ethyl with a saturated solution of $NaHCO_3$ (25 ml), dried (MgSO) and evaporated. The crude product was purified by flash chromatography using dichloromethane–hexane 1:1 for elution. Yield: 0.26 g (56%). Oil. ^{1}H NMR: δ 1.12–2.08 (12 H, m), 2.55–2.68 (CH_2, 1 H, J_{gem} 15.8 Hz), 2.90–3.07 (CH_2, 1 H, J_{gem} 15.8 Hz), 3.69–3.80 (CH, m), 5.37 (CH, t, J 3 Hz), 6.77–6.88 (Ar, 2 H, m), 7.01–7.12 (Ar, 2 H, m). ^{13}C NMR: δ 20.6 (CH_2), 24.1 (CH_2), 24.2 (CH_2), 25.7 (CH_2), 27.0 (CH_2), 31.9 (CH_2), 33.5 (CH_2), 75.4 (OCH), 95.1 (OCHO), 116.9 (CH), 120.3 (CH), 122.6 (C), 127.1

(CH), 129.1 (CH), 152.4 (C). High resolution MS: Found 232.1463. Calc. for $C_{15}H_{20}O_2$: 232.1464. MS (EI): 232 (M^+, 37), 150 (100), 133 (25), 108 (6), 83 (4), 67 (6), 55 (12).

1-Chloro-4-(3-butenyloxymethyl)benzene. **13**. $ZnBr_2$ (0.30 g, 1.3 mmol) in dichloromethane (4 ml) was added to a solution of **4d** (0.23 g, 1.3 mmol) and allyltrimethylsilane (0.21 ml, 1.3 mmol) in dichloromethane (2 ml) at 0 °C under N_2. The mixture was warmed to ambient temperature and stirred for 20 h before it was poured into ice–water (10 ml) and extracted with diethyl ether (3 × 2 ml). The dried (MgSO) solution was evaporated and the crude product was purified by flash chromatography using dichloromethane–hexane 1:3 for elution. Yield: 0.15 g (59%). Oil. ^{1}H NMR: δ 2.36–2.47 (CH_2, q, *J* 6.7 Hz), 3.56 (CH_2, t, *J* 6.7 Hz), 4.53 (CH_2, s), 5.06–5.20 (CH_2=, m), 5.78–5.95 (CH=, m), 7.28–7.48 (Ar, 4 H, m). ^{13}C NMR: δ 34.2 (CH_2), 69.7 (OCH_2), 72.1 ($ArCH_2$), 116.5 (CH_2=), 128.5 (CH), 128.9 (CH), 133.2 (C), 135.1 (C), 137.0 (CH=). MS (EI): 198/196 (M^+, 1/3), 161 (17), 127/125 (34/100), 89 (12), 32 (33).

Pentyloxybenzene **14a**.[22] *Method A.* Butyllithium (1.0 ml, 1.0 mmol, 1.0 M in hexane) was added dropwise to a solution of **4a** (90 mg, 0.71 mmol) in diethyl ether (4 ml) at 0 °C. The mixture was stirred at ambient temperature for 36 h before it was poured into ice–water (2 ml), extracted with hexane (5 × 5 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane for elution. Yield: 100 mg (85%).

Method B. A solution of butylmagnesium bromide (5.0 ml, 2.0 mmol, 0.4 M in diethyl ether) was added to a solution of **4a** (200 mg, 1.58 mmol) in diethyl ether (10 ml) at 0 °C under N_2. After 15 min water (5 ml) was added dropwise and the precipitate filtered off. The precipitate was washed with diethyl ether (2 × 15 ml) and the filtrate was extracted with diethyl ether (3 × 15 ml). The combined diethyl ether solution was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane for elution. Yield: 200 mg (77%).

2-Propenyloxybenzene **14b**.[23] Vinylmagnesium bromide (2.5 ml, 2.5 mmol, 1.0 M in THF) was added dropwise to a solution of **4a** (0.25 g, 2.0 mmol) at 0 °C under N_2. The mixture was stirred for 48 h before it was poured into ice–water (10 ml) and extracted into pentane (5 × 5 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using 15% dichloromethane in hexane for elution. Yield: 0.14 g (52%).

1-Chloro-4-(pentyloxy)methylbenzene **14c**. *Method A.* Butyllithium (1.9 ml, 2.1 mmol, 1.3 M in hexane) was added to a solution of **4c** (0.16 g, 1.5 mmol) in diethyl ether (4 ml) at −78 °C under N_2. The mixture was stirred at ambient temperature for 2 h and poured into ice–water (10 ml), extracted into diethyl ether (3 × 10 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using dichloromethane–hexane 1:29 for elution. Yield: 0.21 g (66%).

Method B. A solution of butylmagnesium bromide (5.0 ml, 2.0 mmol, 0.4 M in diethyl ether) was added to a solution of **4c** (0.12 g, 0.7 mmol) in diethyl ether (3 ml) at −78 °C under N_2. The mixture was stirred at ambient temperature for 12 h, poured into ice–water and the precipitate filtered off. The precipitate was washed with diethyl ether (2 × 3 ml) and the filtrate was extracted with diethyl ether (3 × 10 ml). The combined diethyl ether solution was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using dichloromethane–hexane 1:29 for elution.

Yield: 0.10 g (67%). ^{1}H NMR: δ 0.86–0.94 (CH_3, m), 1.30–1.38 (CH_2, 4 H, m), 1.58–1.65 (CH_2, m), 3.45 (OCH_2, t, J 6.6 Hz), 7.25–7.34 (Ar, 4 H, m). ^{13}C NMR: δ 14.0 (CH_3), 22.5 (CH_2), 28.4 (CH_2), 29.4 (CH_2), 70.7 (OCH_2), 72.1 ($ArCH_2O$), 128.5 (CH), 128.9 (CH), 133.2 (C), 137.3 (C). MS (EI): 214/212 (M^+, 2/5), 197 (8), 140.9 (8), 127/125 (36/100), 91 (20), 77 (9), 69 (24), 43 (37).

1-Chloro-4-(2-propenyloxymethyl)benzene **14d**.[24] A solution of vinylmagnesium bromide (1.0 ml, 1.0 mmol, 1.0 M in THF) was added to a solution of **4d** (100 mg, 0.6 mmol) in diethyl ether (2 ml) at −78 °C under N_2. The mixture was stirred for 12 h, during which time it reached ambient temperature, poured into ice–water and filtered. The solid material was washed with diethyl ether (2 × 2 ml) and the filtrate was extracted with diethyl ether (3 × 7 ml). The combined diethyl ether solution was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using dichloromethane–hexane 15:85 for elution. Yield: 70 mg (64%).

3,4-Dihydro-2-butyl-2H-1-benzopyran **15a**. A solution of butylmagnesium bromide (5.0 ml, 2.0 mmol, 0.4 M in diethyl ether) was added to a solution of **8** (110 mg, 0.7 mmol) in diethyl ether (3 ml) at 0 °C under N_2. The mixture was stirred at ambient temperature for 12 h, poured into ice–water and the precipitate filtered off. The precipitate was washed with diethyl ether (2 × 3 ml) and the filtrate was extracted with diethyl ether (3 × 10 ml). The combined diethyl ether solution was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane for elution. Yield: 80 mg (60%). ^{1}H NMR: δ 0.94 (CH_3, t, *J* 6.7 Hz), 1.25–1.85 (CH_2, 7 H, m) 1.92–2.13 (CH_2, m), 2.65–2.94 (CH_2, m), 4.00–4.31 (OCH, m) 6.76–6.85 (Ar, 2 H, m), 7.00–7.12 (Ar, 2 H, m). ^{13}C NMR: δ 14.1 (CH_3), 22.7 (CH_2), 24.8 (CH_2), 27.3 (CH_2), 27.5 (CH_2), 35.1 (CH_2), 75.9 (CH), 116.7 (CH), 119.82 (CH), 122.09 (C), 127.08 (CH), 129.48 (CH),

155.07 (C). High resolution MS: Found 190.1358. Calc. for $C_{13}H_{18}O$: 190.1358. MS (EI): 190 (M^+, 39), 133 (34), 120 (18), 107 (100), 91 (7), 77 (10).

*3,4-Dihydro-2-ethenyl-2*H*-1-benzopyran* **15b**. A solution of vinylmagnesium bromide (5.0 ml, 5.0 mmol, 1.0 M in THF) was added to a solution of **8** (0.50 g, 3.3 mmol) in diethyl ether (2 ml) at 0 °C under N_2. The mixture was stirred for 7 h, during which time it reached ambient temperature, poured into ice–water and filtered. The solid material was washed with diethyl ether (2 × 5 ml) and the filtrate was extracted with diethyl ether (3 × 5 ml). The combined diethyl ether solution was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using dichloromethane–hexane 1 : 9 for elution. Yield: 0.20 g (42%). ^{1}H NMR: δ 1.72–1.91 (CH_2, 1 H, m), 1.98–2.11 (CH_2, 1 H, m), 2.69–2.84 ($ArCH_2$, m), 4.48–4.58 (OCH, m), 5.18–5.25 (CH_2=, J_{B-A} 10.5 Hz, J_{gem} 1.4 Hz), 5.31–5.41 (CH_2=, J_{C-A} 17.2 Hz, J_{gem} 1.4 Hz), 5.88–6.05 (CH=,dd, J_{A-C} 17.2 Hz, J_{A-B} 10.5 Hz), 6.77–7.12 (Ar, 4 H, m). ^{13}C NMR: δ 24.6 ($ArCH_2$), 27.9 (CH_2), 76.6 (CH), 116.6 (CH_2=), 117.3 (CH), 120.6 (CH), 122.2 (C), 127.8 (CH), 130.0 (CH), 138.1 (CH=), 155.0 (C). High resolution MS: Found 160.0872. Calc. for $C_{11}H_{12}O$: 160.0888. MS (EI) 160 (M^+, 100), 146 (59), 131 (36), 119 (28), 91 (37), 78 (54), 51 (18), 39 (20).

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