Opposite Regioselectivity in the Sequential Ring-Opening of 2-(Alkanoyloxymethyl)aziridinium Salts by Bromide and Fluoride in the Synthesis of Functionalized β-Fluoro Amines

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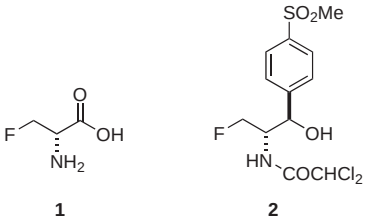
Abstract: 1-Arylmethyl-2-(bromomethyl)aziridines were converted into the corresponding 2-(alkanoyloxymethyl)aziridines upon treatment with potassium 2-methylpropanoate or potassium 2-methylbutyrate in DMSO in excellent yields, following regioselective ring-opening towards *N*-(2-bromo-3-alkanoyloxypropyl)amines using allyl bromide or an arylmethyl bromide in acetonitrile. Treatment of the latter β-bromo amines with tetrabutylammonium fluoride in acetonitrile afforded 2-amino-1-fluoropropanes as the major compounds (72–86%) besides the isomeric 1-amino-2-fluoropropanes in minor quantities (14–28%). The ring-opening of the intermediate aziridinium salts by bromide and fluoride in acetonitrile resulted in a different regioselectivity with a preferential attack of bromide at the more hindered carbon atom and of fluoride at the less hindered carbon atom of the aziridinium ion.

Key words: 2-(bromomethyl)aziridines, aziridinium salts, β-fluoro amines, ring-opening, substitution

1,2,3-Triheteroatom-substituted propane derivatives constitute very valuable target compounds in medicinal chemistry due to the pronounced physiological activities ascribed to many representatives of this class of compounds.[1] In recent years, the introduction of a fluoro atom in a strategic position of a molecule is emerging as a powerful and versatile tool for the development of effective drugs and agrochemicals, since fluorine can dramatically alter both the chemical and the biological properties of these compounds.[2] For example, fluorinated amino acids – such as 3-fluoro-D-alanine (**1**) – and other fluoro amines have received a lot of attention due to their interesting biological activities.[3] Moreover, the incorporation of a β-fluoro amine moiety into a 1,2,3-triheteroatom-substituted propane skeleton has led to the discovery of a new class of powerful antimicrobial agents,[4] with florfenicol (**2**)[4a,4b] as an important example (Figure 1). Nevertheless, synthetic approaches towards 2-amino-3-fluoro-1-oxypropanes are rather limited and restricted mainly to patent literature, with only a few exceptions,[5] despite of the great biological potential of compounds bearing such a moiety in their structure. Therefore, the synthesis of novel 1,2,3-triheteroatom-substituted propane derivatives bearing a fluoro atom is of potential interest.



1 **2**

Figure 1

In this communication, the synthesis of fluorinated propylamines is disclosed based on the sequential ring-opening of the same intermediate aziridinium salts by bromide and fluoride. A comparative study of the ring-opening of these aziridinium salts in acetonitrile showed a different regioselectivity depending on the nature of the nucleophilic halide ion.

1-Arylmethyl-2-(bromomethyl)aziridines **3** are very easily accessible substrates suitable for various applications in organic synthesis, prepared from the corresponding benzaldehydes in a three-step procedure.[6] These 2-(bromomethyl)aziridines **3** are excellent precursors for the synthesis of 1,2,3-trisubstituted propane derivatives since their structure comprises a three-carbon unit in which the three electrophilic carbon atoms are structurally differentiated from each other, allowing the preparation of different substituted propylamines.

1-Arylmethyl-2-(bromomethyl)aziridines **3a**–**d** were converted into the corresponding 2-(alkanoyloxymethyl)aziridines **4a**–**d** upon treatment with one equivalent of potassium 2-methylpropanoate or potassium 2-methylbutyrate in DMSO in excellent yields after heating at 80 °C for 15 hours (Scheme 1).[7] In the case of 2-methylbutyrate (**4d**), the two diastereomers (ratio 47:53) appeared to be inseparable by chromatography (GC and flash) and the mixture was used as such. 2-(Alkanoyloxymethyl)aziridines, mainly 2-(acetyloxymethyl)aziridines, have been prepared in other ways, usually by (enzymatic) acetylation of 2-(hydroxymethyl)aziridines[8] or by ring-closure of mesylated or tosylated 1-acetoxy-2-amino-3-hydroxypropanes.[9] This is the first report of the synthesis of 2-(alkanoyloxymethyl)aziridines starting from 2-(bromomethyl)aziridines in a very efficient procedure based on a simple substitution of the halogen by a nucleophilic carboxylate anion.

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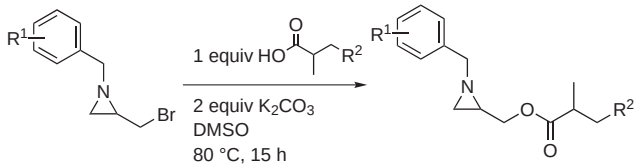


3a (R^1 = 3-Me)
3b (R^1 = 2-Cl)
3c (R^1 = 4-Me)
3d (R^1 = H)

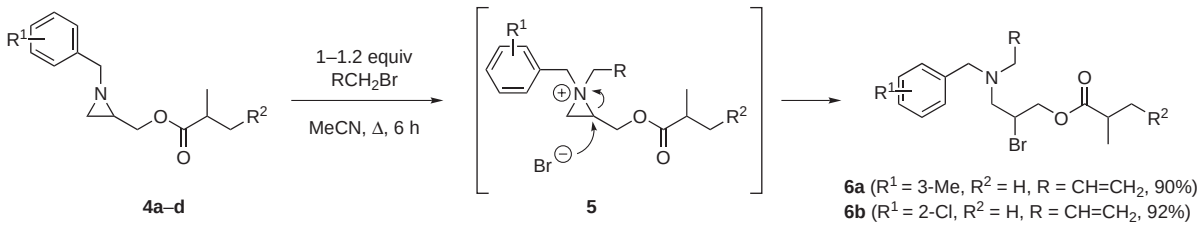
4a (R^1 = 3-Me, R^2 = H, 85%)
4b (R^1 = 2-Cl, R^2 = H, 82%)
4c (R^1 = 4-Me, R^2 = H, 86%)
4d (R^1 = H, R^2 = Me, 77%)

Scheme 1

1-Arylmethyl-2-(bromomethyl)aziridines and 1-arylmethyl-2-(aryloxymethyl)aziridines can be transformed regioselectively into *N*-(2-bromopropyl)amines upon treatment with a benzyl bromide in acetonitrile in a straightforward reaction.[10] Accordingly, 2-(alkanoyloxymethyl)aziridines **4a**–**d** were treated with allyl bromide or an arylmethyl bromide in MeCN and thus converted into the corresponding *N*-(2-bromo-3-alkanoyloxypropyl)amines **6a**–**f** in high yields and high purity after reflux for 6 hours (Scheme 2).[11] Detailed spectral analysis confirmed the structural identity of these novel *N*-(2-bromo-3-alkanoyloxypropyl)amines **6**, excluding the formation of the corresponding regioisomers. Obviously, the intermediate aziridinium salts **5** are opened exclusively at the more hindered aziridine carbon atom by bromide in MeCN towards β-bromo amines **6**. This can be explained considering the weakening of the C_2–N bond upon attack by bromide, resulting in a stable transition state,[10c] followed by ring-opening towards β-bromo amines **6**.

Subsequently, the latter β-bromo amines **6a**–**f** were treated with 1–2 equivalents of tetrabutylammonium fluoride ($TBAF{\cdot}3H_2O$) in acetonitrile, affording a mixture of β-fluoro amines **7** as the major constituents (72–86%) and β-fluoro amines **8** as the minor compounds (14–28%) after reflux for 7 hours (Scheme 3, Table 1).[12] Only in the case of allylamines **7a**/**8a** and **7b**/**8b** (R = CH=CH_2), both regioisomers could be separated by means of column chromatography on silica gel. The presence of the major regioisomers **7**, in which the amino moiety has moved from the terminus of the propane skeleton towards the central carbon atom, can only be rationalized considering the formation of an intermediate aziridinium ion **5** upon heating (Scheme 3), which is then attacked by fluoride at the less hindered carbon atom of the aziridine ring. The formation of the minor isomers **8** can be the result of the attack of fluoride at the more hindered carbon atom of the aziridinium ion **5** or, alternatively, the result of an S_N2 substitution reaction at the bromomethine moiety in bromo amines **6**.

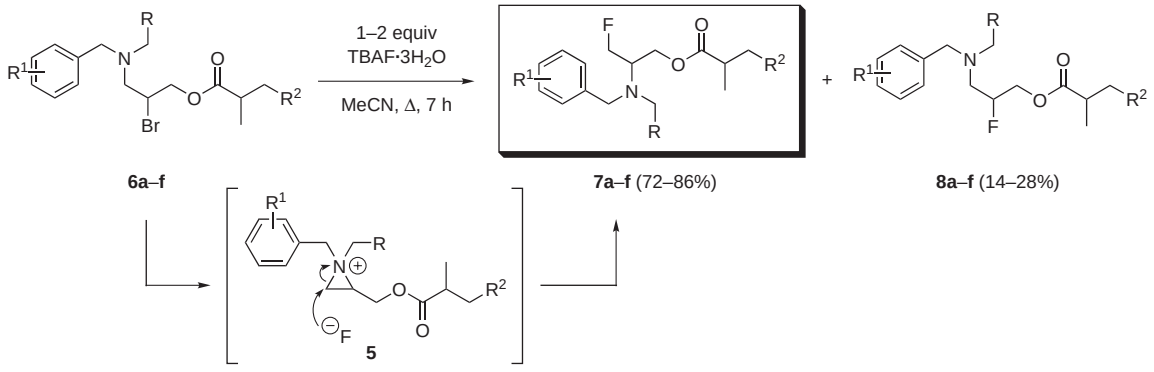
If another fluoride source was used, e.g. potassium fluoride, β-bromo amines **6** were recovered completely upon treatment with one equivalent of KF in refluxing acetonitrile for 7 hours, pointing to the importance of the choice of the fluoride source. The amount of TBAF used for this



4a–d → **5**

6a (R^1 = 3-Me, R^2 = H, R = CH=CH_2, 90%)
6b (R^1 = 2-Cl, R^2 = H, R = CH=CH_2, 92%)
6c (R^1 = 3-Me, R^2 = H, R = Bn, 89%)
6d (R^1 = 4-Me, R^2 = H, R = Bn, 90%)
6e (R^1 = H, R^2 = Me, R = 4-BrC_6H_4, 82%)
6f (R^1 = H, R^2 = Me, R = 4-MeC_6H_4, 85%)

Scheme 2



6a–f → **7a–f** (72–86%) + **8a–f** (14–28%)

5

Scheme 3

Table 1 Conversion of β-Bromo Amines **6** into β-Fluoro Amines **7** and **8** upon Treatment with TBAF in Acetonitrile under Reflux for 7 Hours

Entry	Compounds	R^1	R^2	R	TBAF (equiv)	Ratio **7**.**8**[a]
1	**7a**, **8a**	3-Me	H	$CH=CH_2$	2.0	72:28
2	**7b**, **8b**	2-Cl	H	$CH=CH_2$	2.0	78:22
3	**7c**, **8c**	3-Me	H	Ph	1.5	86:14
4	**7d**, **8d**	4-Me	H	Ph	1.5	77:23
5	**7e**, **8e**	H	Me	$4\text{-}BrC_6H_4$	1.0	77:23
6	**7e**, **8e**	H	Me	$4\text{-}BrC_6H_4$	1.5	83:17
7	**7e**, **8e**	H	Me	$4\text{-}BrC_6H_4$	2.0	79:21
8	**7f**, **8f**	H	Me	$4\text{-}MeC_6H_4$	1.0	74:26
9	**7f**, **8f**	H	Me	$4\text{-}MeC_6H_4$	1.5	86:14
10	**7f**, **8f**	H	Me	$4\text{-}MeC_6H_4$	2.0	79:21

[a] Ratio determined by ^{19}F NMR and ^{1}H NMR.

transformation had a peculiar influence on the ratio of the major versus the minor isomer, since treatment of β-bromo amine **6e** with TBAF (1.0, 1.5 and 2 equiv, respectively), gave mixtures of the corresponding fluoro amines **7e** and **8e** in a 77:23, 83:17 and 79:21 ratio (entries 5, 6 and 7, Table 1). This small shift in favor of the major isomers **7** utilizing 1.5 equivalents of TBAF was also observed upon treatment of β-bromo amines **6f** with TBAF (1.0, 1.5 and 2 equiv, respectively, entries 8, 9 and 10, Table 1), although in both cases the differences are to small to be significant. When dichloromethane was used as the solvent instead of acetonitrile for the conversion of β-bromo amines **6** into β-fluoro amines **7** and **8** upon treatment with TBAF, the ratio of **7**:**8** dropped to 65:35, whereas in THF similar ratios as compared to the reaction in acetonitrile were obtained.

The ring-opening of aziridinium salts by halides constitutes a very powerful method towards the preparation of β-halo amines and, consequently, many synthetic efforts have been devoted to this matter.[13] Interestingly, the regioselectivity of these reactions often appears to be dependent on several factors such as the substrate, the nucleophile and the solvent. Indeed, also in this case, it should be stressed that the same aziridinium salts **5** are present as intermediates in both transformations (Scheme 2 and Scheme 3), although a different regioselectivity upon ring-opening by bromide and fluoride has been observed. Apparently, these aziridinium salts are opened exclusively at the more hindered aziridine carbon atom by bromide and mainly at the less hindered aziridine carbon atom by fluoride, both in acetonitrile. The difference in polarizability between bromide and fluoride can account for this behavior, since the high polarizability of bromide enables the formation of a favorable transition state, stabilized by acetonitrile, upon attack at the substituted aziridine carbon atom, whereas the low polarizability of fluoride impede such a stabilizing interaction, hence the preferential attack at the unsubstituted carbon atom of the intermediate aziridinium salt. The favorable transition state upon attack of bromide has been acknowledged previously by means of high level ab initio calculations for an analogous substrate.[10c] The peculiar behavior of ring-opening reactions of aziridinium salts by fluoride has also been noted before by others, although in these cases ring-opening of N–H or N-activated aziridines by fluoride (upon treatment with HF or Olah's reagent) usually occurred at the more hindered aziridine carbon atom instead of at the less hindered carbon atom.[14]

In conclusion, a novel and easy access towards fluorinated 1-(alkanoyloxy)propylamines has been developed based on the subsequent ring-opening of intermediate aziridinium salts by bromide and fluoride with a different regioselectivity. Further studies on the ring-opening of 2-substituted aziridinium salt are currently in progress, about which will be communicated in due course.

Acknowledgment

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(7) As a representative example, the synthesis of 1-(3-methylbenzyl)aziridin-2-ylmethyl 2-methylpropanoate **4a** is described. To a solution of isobutyric acid (0.88 g, 1.0 equiv) in DMSO (15 mL) was added K_2CO_3 (2.76 g, 2 equiv), and the resulting suspension was stirred for 30 min at r.t. Subsequently, 2-(bromomethyl)-1-(3-methylbenzyl)-aziridine (**3a**, 2.40 g, 0.01 mol) was added, and the mixture was heated at 80 °C for 15 h. The reaction mixture was poured into H_2O (20 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(3-methylbenzyl)aziridin-2-ylmethyl 2-methylpropanoate (**4a**), which was purified by filtration through silica gel (hexane–EtOAc, 5:3).
1-(3-Methylbenzyl)aziridin-2-ylmethyl 2-methylpropanoate (**4a**): R_f = 0.25; light-yellow oil; yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 and 1.11 [6 H, 2 d, *J* = 6.9 Hz, (CH_3)$_2$CH], 1.51 [1 H, d, *J* = 6.3 Hz, (H_{cis}CH)N], 1.77 [1 H, d, *J* = 3.3 Hz, (HCH_{trans})N], 1.82–1.89 (1 H, m, NCH), 2.34 (3 H, s, CH_3Ar), 2.47 [1 H, sept, *J* = 7.0 Hz, (CH_3)$_2$C*H*], 3.30 and 3.53 [2 H, 2 d, *J* = 13.3 Hz, N(HCH)Ar], 3.81 and 4.20 [2 H, 2 × dd, *J* = 11.6, 7.4, 4.5 Hz, (HCH)O], 7.06–7.24 (4 H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.89 [(CH_3)$_2$CH], 21.39 (CH_3Ar), 31.76 [($H_{cis}CH_{trans}$)N], 33.86 [(CH_3)$_2$*C*H], 37.21 (CHN), 64.40 (NCH_2Ar), 66.55 (CH_2O), 125.14, 127.87, 128.27 and 128.85 (HC_{arom}), 137.93 and 138.73 (2 × $C_{arom,quat}$), 176.99 (CO). IR (NaCl): 1733 cm^{-1} (C=O). MS (70 eV): *m*/*z* (%) = 247 (19) [M$^+$], 160 (38), 158 (17), 105 (100), 72 (21), 71 (38). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.97; H, 8.74; N, 5.50.

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(11) As a representative example, the synthesis of 3-[allyl-(3-methylbenzyl)amino]-2-bromopropyl 2-methylpropanoate (**6a**) is described. To a solution of 1-(3-methylbenzyl)-aziridin-2-ylmethyl 2-methylpropanoate (**4a**, 2.47 g, 10 mmol) in MeCN (50 mL) was added allyl bromide (1.45 g, 1.2 equiv) under stirring, and the resulting mixture was heated for 6 h under reflux. Evaporation of the solvent afforded 3-[allyl(3-methylbenzyl)amino]-2-bromopropyl 2-methylpropanoate (**6a**), which was purified by means of column chromatography (hexane–EtOAc, 49:1) on silica gel in order to obtain an analytically pure sample.
3-[Allyl(3-methylbenzyl)amino]-2-bromopropyl 2-methylpropanoate (**6a**): colorless liquid; yield 90%; R_f = 0.04 (hexane–EtOAc, 49:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 [6 H, d, *J* = 7.2 Hz, (CH_3)$_2$CH], 2.34 (3 H, s, CH_3Ar), 2.54 [1 H, sept, *J* = 7.0 Hz, (CH_3)$_2$C*H*], 2.84 and 2.93 [2 H, 2 × dd, *J* = 13.7, 8.8, 5.9 Hz, N(*HCH*)CHBr], 3.06 and 3.17 [2 H, 2 × dd, *J* = 14.0, 6.9, 6.1 Hz, N(*HCH*)CH=CH_2], 3.53 and 3.67 [2 H, 2 d, *J* = 13.5 Hz, N(HCH)Ar], 4.07–4.16 (1 H, m, CHBr), 4.27 and 4.50 [2 H, 2 × dd, *J* = 11.9, 6.3, 3.7 Hz, (HCH)O], 5.15–5.22 (2 H, m, CH=CH_2), 5.79–5.92 (1 H, m, C*H*=CH_2), 7.05–7.26 (4 H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.87 and 18.96 [(CH_3)$_2$CH], 21.41 (CH_3Ar), 33.94 [(CH_3)$_2$*C*H], 48.77 (CHBr), 57.50, 57.67 and 59.12 (3 × CH_2N), 65.70 (CH_2O), 118.07 (CH=*C*H_2), 125.93, 127.95, 128.25 and 129.61 (HC_{arom}), 135.23 (*C*H=CH_2), 137.90 and 138.70 (2 × $C_{arom,quat}$), 176.48 (CO). IR (NaCl): 1736 cm^{-1} (C=O). MS (70 eV): *m*/*z* (%) = 368, 370 (23) [M$^+$ + 1], 288 (100) [M$^+$ – Br]. Anal. Calcd for $C_{18}H_{26}BrNO_2$: C, 58.70; H, 7.12; N, 3.80. Found: C, 58.91; H, 7.31; N, 3.66.

(12) As a representative example, the synthesis of 2-[allyl(3-methylbenzyl)amino]-3-fluoropropyl 2-methylpropanoate (**7a**) and 3-[allyl(3-methylbenzyl)amino]-2-fluoropropyl 2-methylpropanoate (**8a**) is described. To a solution of 3-[allyl-(3-methylbenzyl)amino]-2-bromopropyl 2-methylpropanoate (**6a**, 3.68 g, 10 mmol) in MeCN (50 mL) was added TBAF·3H_2O (4.73 g, 1.5 equiv) under stirring and the resulting mixture was heated for 7 h under reflux. Extraction with H_2O (40 mL) and Et_2O (3 × 30 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 2-[allyl(3-methylbenzyl)amino]-3-fluoropropyl 2-methylpropanoate (**7a**, 72%) and 3-[allyl(3-methylbenzyl)amino]-2-fluoropropyl 2-methylpropanoate (**8a**, 28%). Both isomers were separated by means of column chromatography (hexane–ethyl acetate, 34:1) in order to obtain analytically pure samples.
2-[Allyl(3-methylbenzyl)amino]-3-fluoropropyl 2-methylpropanoate (**7a**): colorless liquid; R_f = 0.16 (hexane–EtOAc, 34:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 and 1.19 [6 H, 2 d, *J* = 6.9 Hz, (CH_3)$_2$CH], 2.34 (3 H, s, CH_3Ar), 2.57 [1 H, sept, *J* = 7.0 Hz, (CH_3)$_2$C*H*], 3.20–3.35 (3 H, m, CHN and NCH_2CH=CH_2), 3.73 and 3.76 [2 H, 2 d, *J* = 14.3 Hz, N(HCH)Ar], 4.20 [1 H, dd, *J* = 11.4, 6.5 Hz, (*H*CH)O], 4.30 [1 H, ddd, *J* = 11.4, 6.5, 1.2 Hz, (HC*H*)O], 4.50 and 4.66 [2 H, dd, *J* = 47.5, 5.1 Hz, (HCH)F], 5.09–5.24 (2 H, m, CH=CH_2), 5.73–5.86 (1 H, m, C*H*=CH_2), 7.04–7.32 (4 H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 19.06 [(CH_3)$_2$CH],

21.52 (CH_3Ar), 34.12 [$(CH_3)_2CH$], 54.06 and 54.81 ($2 \times CH_2N$), 56.85 (d, J = 18.5 Hz, CHN), 61.55 (d, J = 5.8 Hz, CH_2O), 82.34 (d, J = 171.9 Hz, CH_2F), 117.28 ($CH=CH_2$), 125.57, 127.82, 128.26 and 129.22 (HC_{arom}), 136.84 ($CH=CH_2$), 137.94 and 139.87 ($2 \times C_{arom,quat}$), 176.92 (CO). ^{19}F (CCl_3F): δ = –227.42 (td, J = 46.0, 22.4 Hz, CH_2F). IR (NaCl): 1738 cm^{-1} (C=O). MS (70 eV): *m*/*z* (%) = 307 (1) [M^+], 274 (5) [$M^+ - CH_2F$], 206 (45), 174 (40), 105 (100). Anal. Calcd for $C_{18}H_{26}FNO_2$: C, 70.33; H, 8.53; N, 4.56. Found: C, 70.50; H, 8.70; N, 4.41.

3-[Allyl(3-methylbenzyl)amino]-2-fluoropropyl 2-methylpropanoate (**8a**): colorless liquid; R_f = 0.09 (hexane–EtOAc, 34:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 [6 H, d, J = 7.2 Hz, $(CH_3)_2CH$], 2.34 (3 H, s, CH_3Ar), 2.55 [1 H, sept, J = 7.0 Hz, $(CH_3)_2CH$], 2.74 (2 H, dd, J = 19.8, 5.5 Hz, NCH_2CHF), 3.15 (2 H, d, J = 6.3 Hz, $NCH_2CH=CH_2$), 3.62 (2 H, s, NCH_2Ar), 4.11–4.34 (2 H, m, CH_2O), 4.76 (1 H, dddd, J = 48.8, 11.7, 5.8, 3.0 Hz, CHF), 5.14–5.23 (2 H, m, $CH=CH_2$), 5.85–5.93 (1 H, m, $CH=CH_2$), 7.04–7.25 (4 H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ = 18.92 [$(CH_3)_2CH$], 21.42 (CH_3Ar), 33.88 [$(CH_3)_2CH$], 53.39 (d, J = 23.1 Hz, NCH_2CHF), 57.82 ($NCH_2CH=CH_2$), 59.13 (NCH_2Ar), 64.42 (d, J = 21.9 Hz, CH_2O), 90.33 (d, J = 173.1 Hz, CHF), 117.96 ($CH=CH_2$), 125.95, 127.89, 128.22 and 129.61 (HC_{arom}), 135.43 ($CH=CH_2$), 137.90 and 138.83 ($2 \times C_{arom,quat}$), 176.80 (CO). ^{19}F (CCl_3F): δ = –189.50 to –189.34 (m, CHF). IR (NaCl): 1736 cm^{-1} (C=O). MS (70 eV): *m*/*z* (%) = 307 (3) [M^+], 174 (99), 105 (100). Anal. Calcd for $C_{18}H_{26}FNO_2$: C, 70.33; H, 8.53; N, 4.56. Found: C, 70.54; H, 8.72; N, 4.32.

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