Synthesis of Two Metabolites of the Antiarrythmicum Amiodarone

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The metabolism of the potent antiarrythmic drug amiodarone (AMI; **1**) has yet not been fully investigated. Recently, *in vitro* experiments revealed that in rabbit-liver microsomes, AMI (**1**) and its main metabolite MDEA (**2**) were biotransformed to the hydroxylated derivatives 3′-OH-AMI (**3**) and 3′-OH-MDEA (**4**), respectively. To establish the chemical structure of **3** and **4**, we developed a total synthesis of these two metabolites of AMI (**1**). ^{1}H- and ^{13}C-NMR Signal assignment from HSQC and HMBC 2D NMR data of synthesized **4** showed that the proposed structure of metabolite **4** is correct. Even the structure of **3** was found to be correct by comparing its HPLC/MS-MS/MS with the data described earlier.

Introduction. – Amiodarone (AMI; **1**) is a potent antiarrythmic and antianginal drug. Unfortunately, the AMI therapy is accompanied by a number of side effects [1]. Because of the lack of knowledge about its metabolism, it is difficult to attach those side effects to certain degradation products. In humans and laboratory animals, the best known metabolite of AMI is the mono-*N*-deethyl-amiodarone (MDEA; **2**) [2]. During long-term therapy, the serum concentrations of this pharmacologically active metabolite are similar to those of AMI. It was shown that cytochrome P450 3A isoforms are involved in the deethylation [3–5]. Recently, it was found that, in rabbit-liver microsomes, both AMI (**1**) and MDEA (**2**) are biotransformed to 3′-OH-AMI[2]) (**3**) and 3′-OH-MDEA[2]) (**4**), respectively [6][7]. To confirm the chemical structure of **3** and **4**, we developed a synthesis of these two new metabolites of amiodarone (**1**).

Synthesis. – For the synthesis of **3** and **4**, we followed the same synthetic strategy. First, the substituted 2-alkylbenzofuran system should be prepared (see *Scheme 1*), which could later be selectively modified at the 3-position by *Friedel–Crafts* acylation. Instead of starting from an intact benzofuran system, we decided to follow the route of *Le Corre* and *Hercouet* [8][9], who started from the triphenylphosphonium salt **5** and an appropriate acid chloride. In our case, a modified procedure [10][11] was used that involved instead of the acid chloride an activated carboxylic acid, which was first coupled to the triphenylphosphonium salt **5** followed by intramolecular *Wittig*

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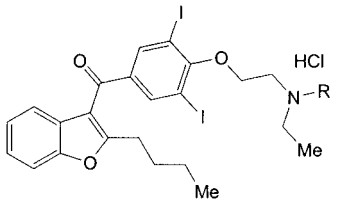
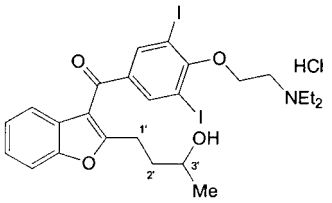
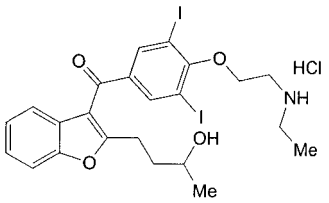
[1]) Part of the planned Ph.D. Thesis of *B. W.*, Universität Zürich.
[2]) The abbreviation 3′-OH-AMI (or 3′-OH-MDEA) stands for the hydroxylated form of amiodarone (or MDEA). The hydroxy function is located at position 3′ of the butyl side chain of the benzofuran unit. The numbering scheme is not in accordance with the *IUPAC* nomenclature.



1·HCl R = Et (AMI·HCl)
2·HCl R = H (MDEA·HCl)



3·HCl (3'-OH-AMI·HCl)[2]



4·HCl (3'-OH-MDEA·HCl)[2]

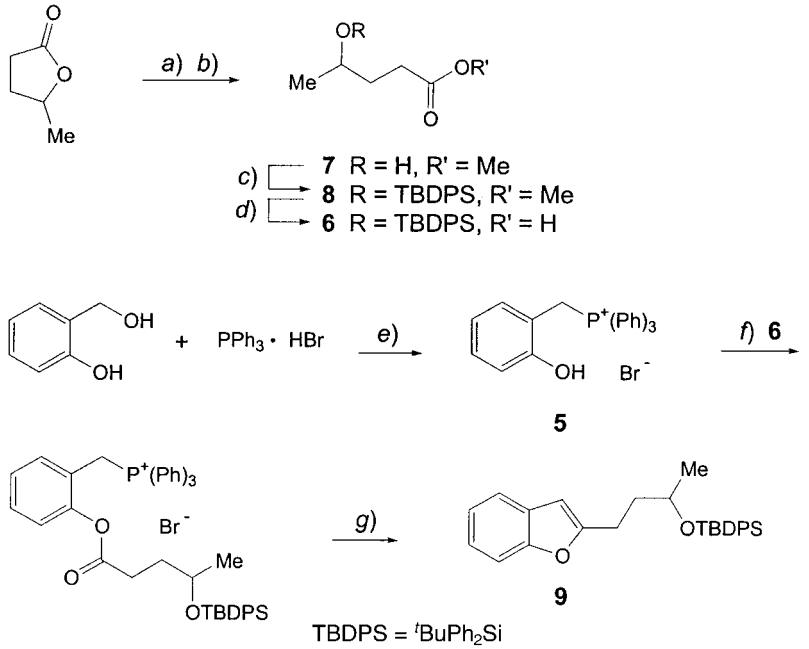
cyclization to the desired benzofuran **9**. The protected 4-hydroxypentanoic acid **6** was synthesized starting from γ-valerolactone (see *Scheme 1*).

Thus, γ-valerolactone was ring-opened and precipitated as its silver salt [12], which was treated with MeI to form methyl 4-hydroxypentanoate (**7**) (73%). The (*tert*-butyl)diphenylsilyl (TBDPS) group was chosen to protect the secondary-alcohol function, bearing in mind that, for the later transformations, a quite stable protecting group towards acidic and basic reaction conditions would be necessary [13]. The optimized procedure for the protection proved to be reaction of **7** with (*tert*-butyl)diphenylsilyl chloride in the presence of 1*H*-imidazole and catalytic amounts of *N*,*N*-dimethylpyridin-4-amine (=dimethylaminopyridine; DMAP) in CH_2Cl_2 to give the ester **8** in 85% yield. Saponification of **8** with aqueous KOH solution in MeOH afforded the desired protected 4-hydroxypentanoic acid **6**.

The triphenylphosphonium salt **5** was prepared in 97% yield starting from triphenylphosphine hydrobromide and 2-hydroxybenzenemethanol [8][9]. Its acylation with **6** by the dicyclohexylcarbodiimide/dimethylaminopyridine (DCC/DMAP) method followed by intramolecular *Wittig* cyclization reaction of the obtained ester with Et_3N produced the benzofuran system **9** substituted at position 2 (76% yield over 2 steps). To obtain pure **9**, it was necessary to repeat the isolation procedure (flash chromatography) at least three times, because **9** tends to be co-eluated with DCC and triphenylphosphine.

The *Friedel–Crafts* acylation of **9** with *p*-anisoyl chloride (=4-methoxybenzoyl chloride) was carried out at 0° with $SnCl_4$ as a *Lewis* acid catalyst [14][15] to give **10** in 72% yield (*Scheme 2*). The catalyst in CH_2Cl_2 was added dropwise. It was very important to keep the reaction at low temperature (0°), because otherwise the TBDPS protecting group was cleaved. With other *Lewis* acids, such as $AlCl_3$ or $FeCl_3$, no reaction took place even at room temperature.

Scheme 1. *Synthesis of the Benzofuran Moiety* **9**



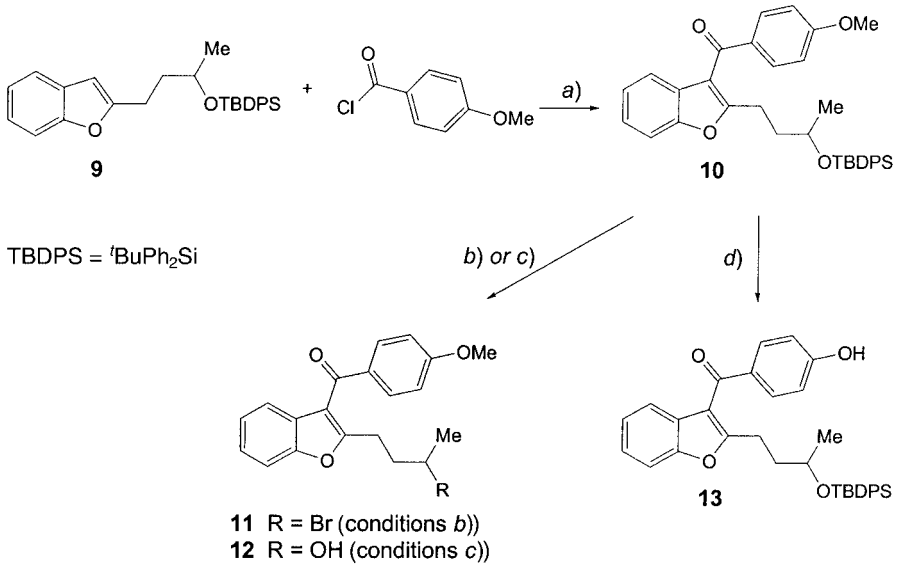
a) Aq. NaOH soln., $AgNO_3$, r.t. *b*) MeI, Et_2O, reflux. *c*) TBDPSCI, 1*H*-imidazole, DMAP, CH_2Cl_2, r.t.; 62% over 3 steps. *d*) Aq. KOH soln., MeOH, reflux; quant. *e*) MeCN, reflux; 97%. *f*) DCC, DMAP, CH_2Cl_2, r.t. *g*) Dioxane, Et_3N, reflux; 76% over 2 steps.

For the demethylation of **10**, different methods were examined. The convenient BBr_3-induced deprotection [16] led only to the substitution product **11**. With other demethylation agents, such as Me_3SiCl/Na_2S [17], pyridinium hydrochloride [15], Me_3SiI [18], or LiI [19], the deprotection also failed to provide **13**. Following *Olah*'s procedure [20] for ether cleavage with *in situ* generated Me_3SiI (from $PhSiMe_3$ and I_2), we obtained **12** in 31% yield. Finally, sodium ethanethiolate in DMF [21] was the reagent of choice to cleave the methyl ether keeping the TBDPS-protected hydroxy function of the side chain intact. With either freshly prepared NaSEt (from Na and EtSH in DMF) or commercially available NaSEt, the reaction provided **13** in good yield (77%). It is important to notice that only the use of freshly prepared NaSEt under strictly O_2-free conditions gave reproducible results.

The iodination of **13** was best achieved with I_2, NaOAc, and NaOH in $MeOH/H_2O$ 1.25:1 to give **14** in quantitative yield [22] (see *Scheme 3*). Having **14** in hand, the phenolic OH group could now be alkylated with either commercial *N*-(2-chloroethyl)-diethylamine hydrochloride (**15**) or with a protected *N*-(2-iodoethyl)ethylamine.

The protected *N*-(2-iodoethyl)ethylamine was synthesized starting from 2-(ethylamino)ethanol (*Scheme 4*). First, the secondary-amino function was quantitatively transformed to carbamate **16** [23] by introducing the (*tert*-butoxy)carbonyl (Boc)

Scheme 2. Friedel–Crafts *Acylation and Methyl Ether Cleavage under Various Conditions*



a) $SnCl_4$, CH_2Cl_2, 0°; 72%. *b*) BBr_3, CH_2Cl_2, −78° → r.t.; 58%. *c*) $PhSiMe_3$, I_2, DMF, 110°; 31%. *d*) NaSEt, DMF, 70°; 77%.

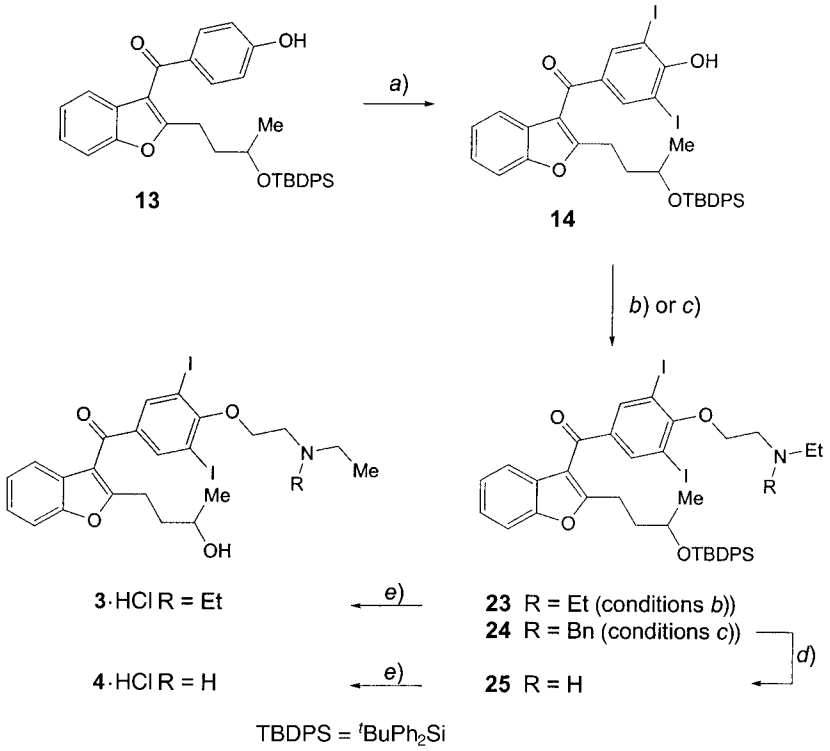
group. To convert the OH group of **16** to the desired halogen substituent, several different procedures were investigated [24–26]. The only product that could be quantitatively isolated was 3-ethyloxazolidin-2-one (**17**). The formation of **17** is promoted by the stability of the *tert*-butyl carbocation; transformation of the primary-alcohol function of **16** into a leaving group leads then to the intramolecular cyclization reaction. Even when the *N*-(2-chloroethyl)ethylamine hydrochloride (**18**)[3]) was tried to be protected with $(Boc)_2O$ in the presence of Et_3N, **17** was exclusively formed. To prevent the formation of **17**, we replaced the Boc group with the (benzyloxy)carbonyl (Z) group. The Z-protected aminoethanol **19** was then transformed into the protected *N*-(2-iodoethyl)ethylamine **20** in low yield. Due to the instability of both carbamates **16** and **19** under the above conditions, we decided to introduce the benzyl protecting group.

After protection of the secondary-amino function with benzyl bromide in the presence of Et_3N in CH_2Cl_2 (→ **21**, 60%), the OH group was converted following the standard procedure [24] to give the *N*-(2-iodoethyl)ethylamine **22** (*Scheme 4*). The yield of this transformation was quite low (19%) due to some side reactions. Nevertheless the coupling of **14** with both amines could now be achieved.

Following the procedure of *Grain* and *Jammot* [22], the alkylation of **14** with either **15** or **22** to **23** and **24**, respectively, was quantitatively achieved in a biphasic system of toluene/H_2O with an excess of K_2CO_3 (*Scheme 3*). Other methods to alkylate the

[3]) For the preparation of **18**, see [27].

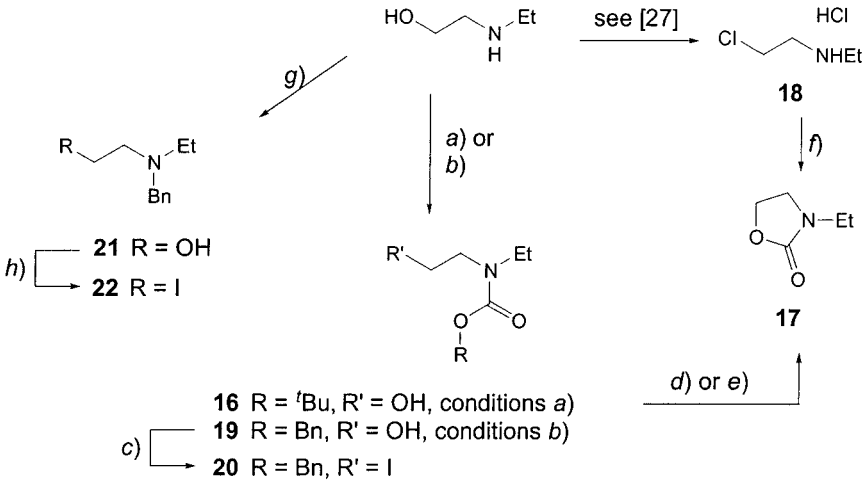
Scheme 3



a) I_2, AcONa, NaOH, MeOH/H_2O 1.25:1, reflux; quant. *b*) K_2CO_3, $Et_2N(CH_2CH_2Cl)\cdot HCl$ (**15**), cat. NaI, toluene/H_2O 2:1, reflux; quant. *c*) K_2CO_3, **22**, toluene/H_2O 2:1, reflux; quant. *d*) 1-Chloroethyl carbonochloridate, 1,2-dichloroethane, reflux, then MeOH, reflux; quant. *e*) Aq. HF soln. (40%), MeCN, r.t. → reflux; **23** → **3**·HCl, 37%; **25** → **4**·HCl, 42%.

phenolic OH group of **14** were investigated, but neither under *Mitsunobu* coupling conditions (DEAD (diethyl diazenedicarboxylate), PPh_3, **19**) [28][29] nor with NaH as a base and **18** [30][31] were the desired products obtained. Having both **23** and **24** in hand, the next steps in the synthesis of **3** and **4** were the deprotection of the 3′-OH group and, in the case of **4**, also the debenzylation of the tertiary-amino function. Because of the diiodophenol moiety, a reductive cleavage of the benzyl group would be problematic. Therefore, we chose 1-chloroethyl carbonochloridate as a dealkylation reagent [32]. The desired **25** with the diiodophenol moiety intact was isolated in very good yield. First attempts to cleave the TBDPS group under standard conditions (Bu_4NF, THF, room temperature) [33] failed because of problems during the purification of **3**, which could not be separated from the excess of Bu_4NF used. The deprotection was then achieved in 37% yield with 40% aqueous HF solution in MeCN [34]. Due to some instability of **3**, column chromatography had to be performed very quickly to avoid decomposition. Even after transformation of **3** into its hydrochloride salt, the compound was very unstable in MeOH. The same deprotection procedure with HF/MeCN was used to access **4**·HCl in 42% yield.

Scheme 4



a) $(Boc)_2O$, CH_2Cl_2, r.t.; quant. *b*) BnO(CO)Cl, K_2CO_3, acetone/H_2O 1:1, 0° → r.t.; 82%. *c*) PPh_3, 1*H*-imidazole, I_2, CH_2Cl_2, r.t.; 29%. *d*) PPh_3, 1*H*-imidazole, I_2, CH_2Cl_2, r.t.; 86%. *e*) PPh_3, Br_2, DMF, r.t.; quant. *f*) $(Boc)_2O$, Et_3N, CH_2Cl_2, r.t.; quant. *g*) BnBr, Et_3N, r.t.; 60%. *h*) Ph_3P, 1*H*-imidazole, I_2, CH_2Cl_2, r.t.; 19%.

Conclusion. – The spectral data (NMR, HPLC/ESI-MS, MS/MS) of our synthesized product and the data of **4** · HCl isolated from rabbit-liver microsomes [6] were found to be identical. The spectral data (HPLC/APCI-MS/MS) of synthetic **3** · HCl also proved to be identical with the other metabolite obtained from degradation of AMI · HCl in rabbit liver microsomes [7].

By means of our synthesis, we established that the hydroxylation of amiodarone (**1**) in rabbit-liver microsomes occurs at the 3′-position of the butyl side chain. Furthermore, the most recent investigations on AMI metabolism in our laboratories indicates that 3′-OH-MDEA (**4**) is present in the plasma of humans receiving AMI · HCl (**1** · HCl) [35]. In contrast, no trace of 3′-OH-AMI (**3**) was detected by HPLC/ESI-MS. With synthesized **3** · HCl and **4** · HCl in hand, the degradation *in vitro* and *in vivo* can be further studied to gain more insight into the AMI metabolism. The pharmacological properties and the toxicity of **3** · HCl and **4** · HCl are currently under investigation and will be published elsewhere.

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Experimental Part

General. All solvents were of anal.-grade quality and were used without further purification unless otherwise stated. THF and Et_2O were dried over Na/benzophenone. DMF was stored over 4 Å molecular sieve under N_2. Flash chromatography (FC): silica gel *Merck 60* (40–63 μm, 230–400 mesh). TLC: *Merck* precoated silica-gel-*60-F*$_{254}$ plates; detection by UV at 254 nm, by *Schlittler* reagent (H_2PtCl_6/HCl/KI), by Ce/Mo reagent ($Ce(SO_4)_2 \cdot 4H_2O$, aq. $H_3[P(Mo_3O_{10})_4]$ soln., aq. H_2SO_4 soln.) or by $KMnO_4$ soln. M.p.: *Mettler FP-5/FP-52*. IR:

Perkin-Elmer 297; in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker ARX-300, DRX-500*, or *AMX-600*; chemical shifts δ in ppm rel. to the internal standard $SiMe_4$ ($CDCl_3$), *J* values in Hz. EI-MS (70 eV), CI-MS (NH_3 as reactant gas) and ESI-MS (NaI/MeOH/CH_2Cl_2): *Finnigan-MAT 90* (EI and CI) and *Finnigan TSQ-700* (ESI); in *m/z* (% of base peak).

(2-Hydroxybenzyl)(triphenyl)phosphonium Bromide (**5**). For the preparation, see [9]. IR ($CHCl_3$): 3670*w*, 3610*m,* 3010*s*, 2960*s*, 3420*w*, 2390*m*, 1630*w*, 1610*w*, 1600*w*, 1510*m*, 1470*m*, 1450*m*, 1430*m*, 1415*m*, 1385*m*, 1330*w*, 1220*s*, 1200*s*, 1110*m*, 1040*m*, 990*w*, 925*m*, 870*m*, 860*m*, 845*m*, 785*s*, 665*s*. ^1H-NMR (300 MHz, $CDCl_3$): 7.76–7.70 (*m*, 3 H); 7.59–7.47 (*m*, 12 H); 7.27–7.30 (*m*, 1 H); 7.01–6.90 (*m*, 2 H); 6.61–6.56 (*m*, 1 H); 4.57 (*d*, *J* = 13.5, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.1 (*s*); 134.7 (*d*); 134.0 (*dd*, *J*(C,P) = 9.5); 130.9 (*d*); 129.9 (*d*); 129.7 (*d*); 119.2 (*d*); 118.1 [*sd*, *J*(C,P) = 84.7); 117.4 (*d*); 113.5 (*sd*, *J*(C,P) = 8.6); 25.6 (*td*, *J*(C,P) = 48.5). EI-MS: 292 (< 1, $[M - Ph]^+$), 262 (52, $[PPh_3]^+$), 183 (100, $[PPh_2]^+$), 152 (16), 107 (30, $[M - CH_2PPh_3]^+$), 77 (39, $[Ph]^+$), 51 (35, $[C_4H_3]^+$).

(±)-Methyl 4-Hydroxypentanoate (**7**). For the synthesis, see [12]. IR (film): 3430*s*, 2965*s*, 1735*s*, 1435*m*, 1370*m*, 1345*m,* 1265*m*, 1170*m*, 1120*m*, 1080*m*, 1030*w*, 955*w*, 940*w*, 895*w*, 845*w*. ^1H-NMR (300 MHz, C_6D_6): 5.49 (br. *s*, 1 H); 3.52–3.46 (*m*, 1 H); 3.32 (*s*, 3 H); 2.28–2.20 (*m*, 2 H); 1.59–1.51 (*m*, 2 H); 0.80 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR (75 MHz, C_6D_6): 174.0 (*s*); 66.9 (*d*); 51.0 (*q*); 34.2 (*t*); 30.5 (*t*); 23.5 (*q*). EI-MS: 132 (< 1, $M^{+\bullet}$), 117 (8, $[M - Me]^+$), 101 (25, $[M - OMe]^+$), 88 (100, $[M - MeCHOH]^+$), 85 (98), 59 (42, $[COOMe]^+$), 57 (56), 56 (59).

*(±)-Methyl 4-{[(*tert*-Butyl)diphenylsilyl]oxy}pentanoate* (**8**). To a soln. of 1*H*-imidazole (6.33 g, 93.00 mmol) and DMAP (0.68 g, 5.57 mmol) in CH_2Cl_2 (40 ml; filtered over neutral Al_2O_3 (act. 1, *Woelm*), **7** (4.92 g, 37.23 mmol) in CH_2Cl_2 (10 ml) was added. After cooling (ice/water), TBDPSCl (10.48 ml, 40.95 mmol) was added within 20 min to this cold mixture. The mixture was allowed to reach r.t. within 6 h and stirred for 12 h at r.t. After quenching with brine (20 ml), the org. layer was separated. The aq. layer was extracted twice with CH_2Cl_2 (2 × 30 ml). The combined org. layer was dried ($MgSO_4$) and evaporated, and the crude product was purified by FC (hexane/AcOEt 30 : 1): pure **8** (11.74 g, 85%). Colorless liquid. IR ($CHCl_3$): 2925*s*, 2880*m*, 2855*s,* 1725*s*, 1460*m,* 1435*s*, 1425*s*, 1370*m*, 1360*m,* 1340*m,* 1295*m*, 1260*m*, 1165*m*, 1130*m*, 1100*s*, 1085*s*, 1005*m*, 995*m*, 940*w*, 900*w*, 815*w*, 680*w*. ^1H-NMR (300 MHz, $CDCl_3$): 7.68–7.65 (*m,* 4 H); 7.43–7.34 (*m*, 6 H); 3.92–3.90 (*m*, 1 H); 3.62 (*s,* 3 H); 2.41–2.35 (*m*, 2 H), 1.82–1.77 (*m*, 2 H); 1.06–1.03 (*d* + *s,* 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.8 (*s*); 135.8 (*d*); 134.6 (*s*); 134.0 (*s*); 129.5 (*d*); 129.4 (*d*); 127.4 (*d*); 127.3 (*d*); 68.5 (*d*); 51.3 (*q*); 34.1 (*t*); 29.7 (*t*); 26.9 (*q*); 22.9 (*q*); 19.2 (*s*). EI-MS: 313 (50, $[M - {}^tBu]^+$), 213 (100), 199 (17, $[OSiPh_2]^+$), 183 (31, $[SiPh_2]^+$).

*(±)-4-{[(*tert*-Butyl)diphenylsilyl]oxy}pentanoic Acid* (**6**). To a soln. of **8** (11.74 g, 31.68 mmol) in EtOH (150 ml), 2M aq. KOH (56 ml, 112.00 mmol) was added. After stirring at r.t. for 14 h, the solvent was evaporated. The white crystalline residue was dissolved in H_2O (20 ml), acidified with conc. aq. HCl soln. to pH ≈ 1, and extracted with Et_2O (3 × 100 ml). The combined org. layer was washed with brine (100 ml), dried ($MgSO_4$), and evaporated. The residue was dried under h.v. for 4 h: pure **6** (11.18 g, 99%). Colorless liquid. IR (film): 3085*m*, 3045*m*, 2960*s*, 2930*s*, 2855*s*, 2660*w*, 1710*s*, 1590*w*, 1470*w*, 1460*w*, 1445*w*, 1425*s*, 1410*w*, 1390*w*, 1380*m*, 1360*w*, 1280*m,* 1260*w*, 1185*w*, 1130*m*, 1110*s*, 1085*s*, 1030*w*, 1020*w*, 1005*w*, 995*m*, 935*w*, 820*m*, 740*m*, 700*s*, 690*m*, 665*w*, 620*w*, 610*s*. ^1H-NMR (300 MHz, $CDCl_3$): 7.69–7.66 (*m*, 4 H); 7.41–7.33 (*m*, 6 H); 3.94–3.92 (*m*, 1 H); 2.46–2.40 (*m*, 2 H); 1.80–1.77 (*m*, 2 H), 1.07–1.04 (*d* + *s*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 179.2 (*s*); 135.8 (*d*); 135.7 (*d*); 134.5 (*s*); 133.9 (*s*); 129.5 (*d*); 129.4 (*d*); 127.5 (*d*); 127.3 (*d*); 68.3 (*d*); 33.7 (*t*); 29.5 (*t*); 26.9 (*q*); 22.8 (*q*); 15.1 (*s*). CI-MS: 357 (100, $[M + H]^+$), 279 (20, $[M - C_6H_5]^+$), 118 (6, $[M - SiPh_2{}^tBu + H]^+$).

*(±)-[3-(Benzofuran-2-yl)-1-methylpropoxy](*tert*-butyl)diphenylsilane* (**9**). Compound **6** (2.655 g, 7.447 mmol) and DCC (3.110 g, 10.152 mmol) were dissolved in CH_2Cl_2 (150 ml), and **5** (3.042 g, 6.770 mmol) and DMAP (83 mg, 0.677 mmol) were added. After stirring at r.t. for 14 h, the mixture was evaporated and the resulting white slurry dissolved in dioxane (150 ml). Et_3N (6.22 ml, 44.626 mmol) was added, and the mixture was refluxed under N_2. After cooling to r.t., the suspension was filtered over *Celite*, the filtrate evaporated, and the residue was suspended in hexane (60 ml). The suspension was filtered over a pad of SiO_2 and evaporated to give the crude product, which was purified by FC (hexane/AcOEt 30 : 1): **9** (2.2 g, 76%). Colorless oil with traces (< 3%) of DCC. IR (film): 3060*m*, 3040*m*, 2960*s*, 2930*s*, 2885*m*, 2850*m*, 1600*w*, 1585*m*, 1470*m,* 1450*s*, 1425*s*, 1385*w*, 1365*m*, 1360*m*, 1250*s*, 1190*w*, 1165*w*, 1130*s*, 1110*s*, 1100*s*, 1080*m*, 1025*m*, 1005*m*, 995*m*, 950*w*, 935*m*, 820*m*, 795*m*, 750*s*, 740*s*, 700*s*, 685*m*, 620*m*, 610*s*. ^1H-NMR (300 MHz, $CDCl_3$): 7.72–7.64 (*m*, 4 H); 7.44–7.30 (*m*, 8 H); 7.19–7.15 (*m*, 2 H); 6.21 (*s*, 1 H); 4.02–3.92 (*m*, 1 H); 2.84–2.78 (*m*, 2 H); 1.98–1.80 (*m*, 2 H); 1.11 (*d*, *J* = 6.1, 3 H); 1.07 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.3 (*s*); 153.6 (*s*); 135.8 (*d*); 134.6 (*s*); 134.0 (*s*); 129.4 (*d*); 129.4 (*d*); 128.8 (*s*); 127.4 (*d*); 127.3 (*d*); 122.9 (*d*); 122.2 (*d*); 120.0 (*d*); 110.6 (*d*); 101.6 (*d*); 68.7 (*d*); 37.0 (*t*); 26.9 (*q*); 24.1 (*t*); 23.0 (*q*); 19.2 (*s*). CI-MS: 207 ($[M - Si{}^tBuPh_2 + NH_4]^+$).

*(±)-[2-(3-{[(*tert*-Butyl)diphenylsilyl]oxy}butyl)benzofuran-3-yl](4-methoxyphenyl)methanone* (**10**). To a cool soln. (ice/water bath) of **9** (1.515 g, 3.534 mmol) and *p*-anisoyl chloride (631 mg, 3.71 mmol) in CH_2Cl_2 (100 ml) in a flame-dried flask under Ar, a pre-cooled 1M $SnCl_4$ soln. in CH_2Cl_2 (3.53 ml, 3.53 mmol) was added dropwise within 25 min. The mixture was stirred at 0° for 5 h, then quenched at 0° by adding brine (20 ml). The aq. layer was separated and extracted with CH_2Cl_2 (2 × 30 ml). The combined org. extract was washed once more with brine (40 ml), dried ($MgSO_4$), and evaporated. The residue was dissolved in CH_2Cl_2 (10 ml), SiO_2 (2 g) was added, and the solvent was carefully distilled off. The crude product now coated on silica gel was purified by FC (hexane/AcOEt 30:1): pure **10** (1.43 g, 72%). Oil which solidified on standing. M.p. 93.3–94.6°. IR ($CHCl_3$): 2955*m*, 2930*m*, 2855*m*, 1640*s*, 1600*s*, 1575*m*, 1510*w*, 1450*m*, 1425*m*, 1375*m*, 1360*m*, 1305*m*, 1280*m*, 1255*s*, 1245*s*, 1170*s*, 1135*m*, 1110*s*, 1070*m*, 1025*m*, 995*m*, 905*s*, 880*m*, 840*m*, 820*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.79 (*d*, *J* = 6.8, 2 H); 7.66–7.62 (*m*, 4 H); 7.45–7.14 (m, 10 H); 6.91 (*d*, *J* = 6.9, 2 H); 3.96–3.89 (*m*, 1 H); 3.84 (*s*, 3 H); 3.07–2.86 (*m*, 2 H); 2.02–1.84 (*m*, 2 H); 1.04 (*d*, *J* = 6.2, 3 H); 1.02 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 190.2 (*s*); 164.1 (*s*); 163.4 (*s*); 153.6 (*s*); 135.8 (*d*); 134.5 (*s*); 134.1 (*s*); 131.8 (*s*); 131.6 (*d*); 129.4 (*d*); 129.4 (*d*); 127.4 (*d*); 127.3 (*d*); 127.2 (*s*); 124.1 (*d*); 123.3 (*d*); 121.2 (*d*); 116.6 (*s*); 113.6 (*d*); 110.8 (*d*); 68.8 (*d*); 55.4 (*q*); 37.3 (*t*); 26.9 (*q*); 24.2 (*t*); 22.8 (*q*); 19.1 (*s*). CI-MS: 563 (100, $[M+H]^+$), 485 (46, $[M-C_6H_5]^+$).

(±)-[2-(3-Hydroxybutyl)benzofuran-3-yl](4-methoxyphenyl)methanone (**12**). A soln. of **10** (45 mg, 0.078 mmol), Me_3SiPh (18 mg, 0.120 mmol) and I_2 (30 mg, 0.118 mmol) in DMF (2 ml) was heated under N_2 to 110° for 8 h. After cooling to r.t., the mixture was hydrolyzed with aq. $NaHCO_3$ soln. (4 ml), Et_2O (10 ml) was added, the aq. layer was separated and, after acidifying with 10% aq. HCl soln. to pH 1, extracted with Et_2O (3 × 10 ml). The combined org. extract was washed with brine (10 ml), dried ($MgSO_4$), and evaporated. Purification by FC (hexane/AcOEt 4:1) gave glass-like **12** (8 mg, 31%). IR (film): 3400*w*, 2970*w*, 2920*w*, 1635*m*, 1600*s*, 1570*s*, 1510*m*, 1470*w*, 1450*m*, 1375*m*, 1310*w*, 1290*m*, 1260*m*, 1245*s*, 1235*w*, 1195*m*, 1180*m*, 1170*s*, 1110*s*, 1070*m*, 1030*m*, 1010*m*, 905*m*, 840*w*, 615*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.88 (*d*, *J* = 8.9, 2 H); 7.58 (*d*, *J* = 9.0, 1 H); 7.31–7.26 (*m*, 1 H); 7.20–7.14 (*m*, 2 H); 6.89 (*d*, *J* = 9.0, 2 H); 3.91 (*s*, 3 H); 3.78–3.67 (*m*, 1 H); 3.30–3.18 (*m*, 1 H); 3.04–2.96 (*m*, 1 H); 2.08–1.81 (*m*, 2 H); 1.21 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 191.1 (*s*); 164.4 (*s*); 163.8 (*s*); 153.6 (*s*); 132.2 (*d*); 131.1 (*s*); 126.6 (*s*); 124.3 (*d*); 123.3 (*d*); 121.1 (*d*); 117.5 (*s*); 113.7 (*d*); 111.1 (*d*); 65.7 (*d*); 55.4 (*q*); 36.8 (*t*); 24.1 (*t*); 22.8 (*q*). CI-MS: 325 ($[M+H]^+$).

(±)-[2-(3-Bromobutyl)benzofuran-3-yl](4-methoxyphenyl)methanone (**11**). To a cooled soln. (−78°) of **10** (10 mg, 0.0178 mmol), 1M BBr_3 in CH_2Cl_2 (20 µl, 0.020 mmol) was added. The mixture was stirred at r.t. for 4 h and then cooled again to 10°, before more 1M BBr_3 in CH_2Cl_2 (40 µl, 0.040 mmol) was added. After stirring for 12 h at r.t., another aliquot of 1M BBr_3 in CH_2Cl_2 (80 µl, 0.080 mmol) was added, and the mixture was kept at r.t. for an additional 3 h. After quenching with ice-water, the aq. phase was extracted with CH_2Cl_2 (10 ml), the combined org. phase was washed with brine, dried ($MgSO_4$), and evaporated. The crude product was purified by FC (hexane/AcOEt 2:1): pure oily **11** (4 mg, 58%). IR (film): 3000*w*, 2960*w*, 2930*w*, 2840*w*, 1640*s*, 1600*s*, 1575*s*, 1510*s*, 1470*m*, 1450*s*, 1440*m*, 1420*m*, 1380*m*, 1370*m*, 1360*m*, 1310*m*, 1290*m*, 1260*s*, 1245*s*, 1180*m*, 1170*s*, 1160*m*, 1110*m*, 1030*m*, 1010*m*, 940*w*, 910*m*, 885*m*, 845*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.87 (*d*, *J* = 8.9, 2 H); 7.52–7.13 (*m*, 4 H); 6.97 (*d*, *J* = 8.9, 2 H); 4.16–4.04 (*m*, 1 H); 3.90 (*s*, 3 H); 3.28–3.00 (*m*, 2 H); 2.33–2.24 (*m*, 2 H); 1.74 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$, one signal missing): 190.2 (*s*); 163.5 (*s*); 162.6 (*s*); 152.5 (*s*); 131.6 (*d*); 126.8 (*s*); 124.3 (*d*); 123.4 (*d*); 121.2 (*d*); 116.0 (*s*); 113.7 (*d*); 110.9 (*d*); 55.4 (*q*); 49.8 (*d*); 39.0 (*t*); 26.6 (*t*); 26.1 (*q*). CI-MS: 387, 389 (41, 42, $[M+1]^+$), 312, 314 (100, 98), 295, 297 (61, 59), 274 (67), 196 (68).

*(±)-[2-(3-{[(*tert*-Butyl)diphenylsilyl]oxy}butyl)benzofuran-3-yl](4-hydroxyphenyl)methanone* (**13**). To a soln. of **10** (1.43 g, 2.54 mmol) in DMF (20 ml), NaSEt (4.27 g, 50.82 mmol) was added. The mixture was heated to 70° for 17 h under N_2. After cooling to 0°, 10% aq. HCl soln. (20 ml) and CH_2Cl_2 (25 ml) were added, and the aq. layer was separated. After extraction with CH_2Cl_2 (2 × 25 ml), the combined org. layer was washed with brine (25 ml), dried ($MgSO_4$), and evaporated. The crude product was dried under h.v. and then purified by FC (hexane/AcOEt 8:1): pure, oily **13** (1.07 g, 77%). IR (film): 3330*m*, 3065*m*, 3020*m*, 2960*s*, 2925*s*, 2880*m*, 2850*m*, 1735*w*, 1705*m*, 1625m, 1600*s*, 1585*s*, 1510*w*, 1470*m*, 1450*m*, 1425*s*, 1375*m*, 1360*m*, 1280*m*, 1245*s*, 1165*s*, 1130*m*, 1110*s*, 1070*m*, 1040*m*, 1010*m*, 995*m*, 935*w*, 905*m*, 884*m*, 845*m*, 820*m*, 780*w*, 750*m*, 740*m*, 700*s*, 610*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.74 (*d*, *J* = 6.7, 2 H); 7.65–7.60 (*m*, 4 H); 7.45–7.13 (m, 10 H); 6.85 (*d*, *J* = 6.7, 2 H); 3.94–3.85 (*m*, 1 H); 3.05–2.85 (*m*, 2 H); 1.97–1.86 (*m*, 2 H); 1.04 (*d*, *J* = 6.1, 3 H); 1.01 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 191.6 (*s*); 164.7 (*s*); 161.0 (*s*); 153.6 (*s*); 135.8 (*d*); 134.5 (*s*); 134.1 (*s*); 132.1 (*d*); 131.1 (*s*); 129.5 (*d*); 129.4 (*d*); 127.6 (*d*); 127.5 (*d*); 127.1 (*s*); 124.3 (*d*); 123.4 (*d*); 121.1 (*d*); 116.6 (*s*); 115.5 (*d*); 110.9 (*d*); 68.8 (*d*); 37.2 (*t*); 26.9 (*q*); 24.2 (*t*); 22.8 (*q*); 19.2 (*s*). CI-MS: 549 (100, $[M+H]^+$), 491 (15, $[M-C_3H_{10}]^+$), 471 (80, $[M-C_6H_5]^+$).

*(±)-[2-(3-{[(*tert*-Butyl)diphenylsilyl]oxy}butyl)benzofuran-3-yl](4-hydroxy-3,5-diiodophenyl)methanone* (**14**). A soln. of **13** (228 mg, 0.415 mmol), $AcONa \cdot 3\,H_2O$ (136 mg, 0.999 mmol), and I_2 (253 mg, 0.997 mmol) in

MeOH (25 ml) was heated to reflux for 45 min. To the cooled soln. was added 0.192M aq. NaOH (5 ml, 0.96 mmol) and H_2O (15 ml). The mixture was then heated to reflux for 2 h, cooled, and stirred at r.t. for 12 h. After quenching with aq. Na_2SO_3 soln. (2.00 g, 19.41 mmol; 10 ml), the solvent was evaporated, and the residue was partitioned between Et_2O (30 ml) and H_2O (20 ml). The aq. layer was extracted with Et_2O (2 × 30 ml), and the combined org. layer was washed with 10% aq. HCl soln. (10 ml), H_2O (10 ml), and brine (30 ml), dried ($MgSO_4$), and evaporated: pure **14** (331 mg, 99%). Yellow crystals. M.p. 47.4–48.7°. IR ($CHCl_3$): 3660*w*, 3460*m*, 3060*m*, 2995*m*, 2950*s*, 2925*s*, 2880*m*, 2850*s*, 1710*w*, 1640*s*, 1585*m*, 1570*s*, 1470*m*, 1450*s*, 1425*s*, 1385*s*, 1360*s*, 1320*m*, 1280*s*, 1185*s*, 1165*s*, 1150*s*, 1130*s*, 1110*s*, 1070*s*, 1020*m*, 1005*m*, 995*m*, 935*m*, 905*s*, 855*m*, 820*s*, 695*s*, 610*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.16 (*s*, 2 H); 7.66–7.61 (*m*, 4 H); 7.47–7.21 (m, 10 H); 3.98–3.90 (*m*, 1 H); 3.08–2.80 (*m*, 2 H); 1.97–1.89 (*m*, 2 H); 1.08 (*d*, *J* = 6.1, 3 H); 1.00 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 187.1 (*s*); 165.1 (*s*); 157.0 (*s*); 153.6 (*s*); 140.6 (*d*); 137.3 (*s*); 135.7 (*d*); 135.7 (*d*); 134.4 (*s*); 133.9 (*s*); 129.5 (*d*); 129.4 (*d*); 127.5 (*d*); 127.3 (*d*); 126.6 (*s*); 124.5 (*d*); 123.7 (*d*); 120.9 (*d*); 116.4 (*s*); 111.00 (*d*); 81.9 (*d*); 68.8 (*d*); 37.1 (*t*); 26.9 (*q*); 24.4 (*t*); 22.9 (*q*); 19.1 (*s*). CI-MS: 801 (22, $[M+H]^+$), 743 (11, $[M-C_3H_{10}]^+$), 723 (100, $[M-C_6H_5]^+$).

*(±)-[2-(3-[[(*tert*-Butyl)diphenylsilyl]oxy}butyl)benzofuran-3-yl][-4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone* (**23**). Compound **14** (331 mg, 0.413 mmol), *N*-(2-chloroethyl)diethylamine hydrochloride (**15**; 78 mg, 0.453 mmol), K_2CO_3 (228 mg, 1.650 mmol), and traces of NaI were dissolved in toluene/H_2O 2:1 (15 ml). The soln. was stirred vigorously and heated to reflux for 5 h. After cooling, the aq. layer was extracted with Et_2O (2 × 15 ml), the combined org. layer was washed with brine (15 ml), dried ($MgSO_4$), and evaporated, and the residue was dried under h.v.: pure **23** (356 mg, 96%). Yellow oil. IR ($CHCl_3$): 2960*s*, 2930*s*, 2870*m*, 2850*s*, 1710*w*, 1655*m*, 1640*s*, 1585*m*, 1570*m*, 1470*m*, 1460*m*, 1450*s*, 1425*m*, 1380*s*, 1280*m*, 1260*s*, 1170*m*, 1135*s*, 1110*s*, 1070*m*, 1010*m*, 995*m*, 945*m*, 890*w*, 855*w*, 840*w*, 820*w*, 695*m*, 660*w*, 610*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.19 (*s*, 2 H); 7.67–7.63 (*m*, 4 H); 7.47–7.21 (*m*, 10 H); 4.13 (*t*, *J* = 6.7, 2 H); 3.94–3.90 (*m*, 1 H); 3.09 (*t*, *J* = 6.7, 2 H); 3.06–2.87 (*m*, 2 H); 2.73 (*q*, *J* = 7.1, 4 H); 1.94–1.91 (*m*, 2 H); 1.12 (*t*, *J* = 7.1, 6 H); 1.07 (*d*, *J* = 6.1, 3 H); 1.02 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 187.4 (*s*); 165.7 (*s*); 161.5 (*s*); 153.6 (*s*); 140.7 (*d*); 138.1 (*s*); 135.7 (*d*); 134.4 (*s*); 133.9 (*s*); 129.5 (*d*); 129.4 (*d*); 127.5 (*d*); 127.3 (*d*); 126.4 (*s*); 124.6 (*d*); 123.7 (*d*); 120.9 (*d*); 115.6 (*s*); 111.0 (*d*); 90.7 (*s*); 71.3 (*t*), 68.7 (*d*); 52.0 (*t*); 47.7 (*t*); 37.0 (*t*); 26.9 (*q*); 24.4 (*t*); 22.8 (*q*); 19.1 (*s*); 11.9 (*q*). CI-MS: 900 (8, $[M+H]^+$), 706 (35), 621 (100). ESI-MS: 900 ($[M+H]^+$).

tert-*Butyl Ethyl-(2-hydroxyethyl)carbamate* (**16**). For the preparation, see [23]. IR (film): 3440*s* (br.), 2980*s*, 2930*s*, 2860*s*, 1770*s*, 1470*s*, 1455*s*, 1410*s*, 1360*s*, 1290*s*, 1250*s*, 1215*m*, 1180*s*, 1150*s*, 1080*s*, 1050*s*, 970*m*, 880*m*, 860*m*, 795*m*, 770*m*, 760*m*, 735*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.72 (*t*, *J* = 5.4, 2 H); 3.35 (*t*, *J* = 5.4, 2 H); 3.26 (*q*, *J* = 7.0, 2 H); 1.45 (*s*, 9 H); 1.10 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$; CO signal missing): 62.3 (*t*); 49.7 (*t*); 43.3 (*t*); 31.1 (*s*); 28.3 (*q*); 13.5 (*q*). CI-MS: 190 ($[M+H]^+$).

Benzyl Ethyl(2-hydroxyethyl)carbamate (**19**). To a soln. of 2-(ethylamino)ethanol (2 ml, 20.51 mmol) in acetone (50 ml), a soln. of K_2CO_3 (5.67 g, 41.02 mmol) in H_2O (50 ml) was added. After cooling to 0°, benzyl carbonochloridate (3.31 g, 21.28 mmol) was added, and the mixture was stirred at r.t. for 12 h. After acidifying with 10% aq. HCl soln. to pH 1, the soln. was extracted with AcOEt (3 × 70 ml). The org. extract was dried ($MgSO_4$) and evaporated, and the residue was dried *in vacuo*: pure, liquid **19** (3.77 g, 82%). IR (film): 3420*s* (br.), 2970*m*, 2930*m*, 2870*m*, 1680*s*, 1475*s*, 1450*s*, 1420*s*, 1365*m*, 1275*s*, 1210*s*, 1150*m*, 1080*m*, 1050*m*, 990*m*, 905*w*, 860*w*, 790*w*, 770*m*, 735*m*, 700*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.26 (*m*, 5 H); 5.14 (*s*, 2 H); 3.75 (*t*, *J* = 5.4, 2 H); 3.43 (*t*, *J* = 5.5, 2 H); 3.36 (*q*, *J* = 7.0, 2 H); 2.74 (br. *s*, 1 H); 1.13 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$; CO signal missing): 136.6 (*s*); 128.4 (*d*); 127.9 (*d*); 127.7 (*d*); 67.1 (*t*); 61.9 (*t*); 50.1 (*t*); 43.2 (*t*); 13.7 (*q*). CI-MS: 224 ($[M+H]^+$).

3-Ethyloxazolidin-2-one (**17**). Prepared as described for **22** from **16** (0.500 g, 2.642 mmol), PPh_3 (832 mg, 3.170 mmol), 1*H*-imidazole (216 mg, 3.170 mmol), and I_2 (805 mg, 3.170 mmol) in CH_2Cl_2 (100 ml). After workup and FC (hexane/AcOEt 3:1 → 0:1), pure, liquid **17** (262 mg, 86%) was isolated. For spectral data, see [36].

Benzyl Ethyl(2-iodoethyl)carbamate (**20**). Prepared as described for **22** from **19** (2 g, 8.958 mmol), PPh_3 (2.82 g, 0.1075 mmol), 1*H*-imidazole (732 mg, 0.1075 mmol), and I_2 (2.73 g, 0.1075 mmol) in CH_2Cl_2 (100 ml). After workup and FC (hexane/AcOEt 20:1 → 4:1), pure, liquid **20** (0.866 g, 29%) was isolated. IR (film): 3060*w*, 3020*w*, 2970*m*, 2930*m*, 2870*w*, 1755*m*, 1700*s*, 1470*s*, 1450*s*, 1415*s*, 1360*m*, 1310*m*, 1275*s*, 1230*m*, 1175*s*, 1110*m*, 1070*m*, 1025*w*, 990*w*, 970*w*, 810*w*, 790*w*, 770*m*, 750*m*, 730*m*, 695*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.46–7.32 (*m*, 5 H); 5.40 (*s*, 2 H); 3.65 (*t*, *J* = 7.5, 2 H); 3.42 (*q*, *J* = 6.8, 2 H); 3.25–3.18 (br. *m*, 2 H); 1.20 (*t*, *J* = 6.9, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$; CO signals missing): 136.6 (*s*); 128.5 (*d*); 128.0 (*d*); 127.8 (*d*); 67.2 (*t*); 49.7 (*t*); 42.8 (*t*); 14.8 (*q*); 1.6 (*t*). CI-MS: 351 (90, $[M+NH_4]^+$), 334 (59, $[M+H]^+$), 224 (26, $[M+NH_4-HI]^+$), 206 (21, $[M+H-HI]^+$), 133 (100), 108 (53), 72.1 (82).

2-[Benzyl(ethyl)amino]ethanol (**21**). To a soln. of 2-(ethylamino)ethanol (3.66 g, 0.041 mmol) and Et_3N (8.30 g, 0.082 mmol) in CH_2Cl_2 (100 ml), BnBr (7.72 g, 0.045 mmol) was added dropwise, and the soln. was

stirred for 14 h at r.t. After quenching with brine (20 ml), the aq. layer was extracted with CH_2Cl_2 (2 × 20 ml), the combined org. layer was dried ($MgSO_4$) and evaporated, and the residue was dried under h.v.: **21** (4.41 g, 60%), pure enough for the next step. IR (film): 3330*s* (br.), 3080*m*, 3060*m*, 3020*m*, 2960*s*, 2960*s*, 2930*s*, 2870*s*, 2800*s*, 1490*m*, 1455*s*, 1370*m*, 1290*m*, 1250*m*, 1210*m*, 1180*m*, 1150*m*, 1075*s*, 1050*s*, 1030*s*, 980*w*, 910*w*, 870*w*, 770*m*, 730*s*, 700*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.35 – 7.20 (*m*, 5 H); 3.64 (*s*, 2 H); 3.56 (*t*, *J* = 5.4, 2 H); 2.66 (*t*, *J* = 5.4, 2 H); 2.58 (*q*, *J* = 7.1, 2 H); 1.06 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.7 (*s*); 128.8 (*d*); 128.3 (*d*); 127.0 (*d*); 58.3 (*t*); 57.7 (*t*); 54.5 (*t*); 47.2 (*t*); 11.6 (*q*). CI-MS: 180 (100, $[M+H]^+$), 148 (22, $[M-MeOH+H]^+$).

Benzyl(ethyl)(2-iodoethyl)amine (**22**). To a soln. of PPh_3 (1.76 g, 6.71 mmol) and 1*H*-imidazole (0.46 g, 6.76 mmol) in CH_2Cl_2 (100 ml), I_2 (1.70 g, 6.69 mmol) was added portionwise. The suspension was stirred till all I_2 was dissolved. Then, **21** (1.00 g, 5.58 mmol) in CH_2Cl_2 (5 ml) was added slowly, and the suspension was stirred for 2 h at r.t. (the flask was wrapped with Al foil to avoid exposure to light). The mixture was quenched with brine (20 ml), the aq. layer was extracted with CH_2Cl_2 (2 × 20 ml), the combined org. extract was dried ($MgSO_4$) and evaporated, and the crude mixture was purified by FC (hexane/AcOEt 1:1): pure **22** (303 mg, 19%). Colorless light-sensitive liquid. IR (film): 2960*s*, 2920*s*, 2800*m*, 1600*m*, 1490*w*, 1450*s*, 1370*m*, 1160*s*, 1100*m*, 1070*m*, 1050*m*, 1025*w*, 900*w*, 695*w*, 660*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.45 – 7.28 (*m*, 5 H); 3.64 (*s*, 2 H); 3.16 (*t*, *J* = 7.7, 2 H); 2.86 (*t*, *J* = 7.7, 2 H); 2.59 (*q*, *J* = 7.1, 2 H); 1.06 (*t*, *J* = 7.1, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 139.4 (*s*); 128.8 (*d*); 128.3 (*d*); 127.0 (*d*); 58.0 (*t*); 56.2 (*t*); 47.5 (*t*); 12.0 (*q*); 4.3 (*t*). CI-MS: 290 ($[M+H]^+$).

*(±)-(4-{2-[Benzyl(ethyl)amino]ethoxy}-3,5-diiodophenyl)[2-(3-{[(*tert*-butyl)diphenylsilyl]oxy}butyl)benzofuran-3-yl]methanone* (**24**). A suspension of **14** (50 mg, 0.0625 mmol), **22** (19 mg, 0.0657 mmol), and K_2CO_3 (26 mg, 0.1875 mmol) in toluene/H_2O 2:1 (9 ml) was stirred vigorously and heated to reflux for 14 h. After cooling, the aq. layer was extracted with Et_2O (2 × 15 ml), the combined org. layer was washed with brine (15 ml), dried ($MgSO_4$), and evaporated, and the yellow residue was dried under h.v. for 3 h: pure **24** (60 mg, 99%). IR ($CHCl_3$): 3130*w*, 2950*m*, 2930*s*, 2880*m*, 2860*m*, 1725*w*, 1655*m*, 1650*s*, 1640*s*, 1600*m*, 1590*m*, 1570*m*, 1560*m*, 1520*w*, 1470*m*, 1460*m*, 1450*s*, 1435*m*, 1425*m*, 1370*s*, 1360*m*, 1280*m*, 1250*m*, 1170*m*, 1130*m*, 1110*s*, 1105*s*, 1070*m*, 1020*m*, 1010*m*, 995*m*, 985*m*, 940*m*, 905*m*, 855*w*, 820*m*, 695*m*, 610*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.15 (*s*, 2 H); 7.68 – 7.60 (*m*, 4 H); 7.43 – 7.17 (*m*, 15 H); 4.07 (*t*, *J* = 6.6, 2 H); 3.95 – 3.85 (*m*, 1 H); 3.76 (*s*, 2 H); 3.07 (*t*, *J* = 6.5, 2 H); 3.04 – 2.78 (*m*, 2 H); 2.69 (*q*, *J* = 7.1, 4 H); 1.96 – 1.83 (*m*, 2 H); 1.12 (*t*, *J* = 7.1, 6 H); 1.07 (*d*, *J* = 6.1, 3 H); 1.02 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 187.5 (*s*); 165.7 (*s*); 161.5 (*s*); 153.6 (*s*); 140.7 (*d*)); 139.5 (*s*); 138.0 (*s*); 135.7 (*d*); 134.4 (*s*); 133.9 (*s*); 129.5 (*d*); 129.4 (*d*); 128.9 (*d*); 128.1 (*d*); 127.5 (*d*); 127.4 (*d*); 126.8 (*d*); 126.4 (*s*); 124.6 (*d*); 123.7 (*d*); 121.0 (*d*); 115.7 (*s*); 111.02 (*d*); 90.8 (*s*); 71.7 (*t*), 68.7 (*d*); 58.7 (*t*); 52.4 (*t*); 48.3 (*t*) 37.0 (*t*); 26.9 (*q*); 24.4 (*t*); 22.9 (*q*); 19.2 (*s*); 12.2 (*q*). ESI-MS: 962 (100, $[M+H]^+$), 984 (16, $[M+Na]^+$).

*(±)-[2-(3-{[(*tert*-Butyl)diphenylsilyl]oxy}butyl)benzofuran-3-yl][4-[2-(ethylamino)ethoxy]-3,5-diiodophenyl]methanone* (**25**). To a suspension of **24** (105 mg, 0.1092 mmol) in 1,2-dichloroethane (5 ml), 1-chloroethyl carbonochloridate (21 mg, 0.1469 mmol) was added under N_2. The mixture was heated to reflux for 2 h. To make sure that no traces of **24** were left, additional 1-chloroethyl carbonochloridate (21 mg, 0.1469 mmol) was added, and the mixture was refluxed for another hour. The solvent was evaporated, and the residue was dissolved in MeOH (5 ml). After heating to reflux for 1 h, the solvent was evaporated and the residue partitioned between CH_2Cl_2 (10 ml) and sat. aq. $NaHCO_3$ soln. The aq. layer was extracted with CH_2Cl_2 (2 × 10 ml). The combined org. layer was washed with brine (15 ml), dried ($MgSO_4$), and evaporated, and the residue was dried under h.v. for 3 h: colorless oil (94 mg, 99%) that solidified. IR ($CHCl_3$): 3060*w*, 2950*s*, 2920*s*, 2850*s*, 1730*w*, 1655*m*, 1640*s*, 1590*m*, 1570*m*, 1525*w*, 1460*m*, 1450*s*, 1435*m*, 1425*m*, 1370*s*, 1360*m*, 1280*m*, 1260*m*, 1240*m*, 1185*m*, 1170*m*, 1130*s*, 1110*s*, 1105*s*, 1070*s*, 1010*m*, 995*m*, 935*m*, 900*w*, 855*w*, 820*m*, 695*m*, 660*m*, 610*m*. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.12 (*s*, 2 H); 7.62 – 7.52 (*m*, 4 H); 7.35 – 7.20 (*m*, 10 H); 4.12 (*t*, *J* = 5.1, 2 H); 3.92 – 3.80 (*m*, 1 H); 3.10 (*t*, *J* = 5.1, 2 H); 3.04 – 2.72 (*m*, 2 H); 2.75 (*q*, *J* = 7.1, 2 H); 1.92 – 1.78 (*m*, 2 H); 1.13 (*t*, *J* = 7.1, 3 H); 0.97 (*d*, *J* = 7.1, 3 H); 0.94 (*s*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 187.4 (*s*); 165.8 (*s*); 160.9 (*s*); 153.6 (*s*); 140.8 (*d*); 138.3 (*s*); 135.7 (*d*); 134.4 (*s*); 133.9 (*s*); 129.5 (*d*); 129.4 (*d*); 127.5 (*d*); 127.4 (*d*); 126.4 (*s*); 124.6 (*d*); 123.8 (*d*); 120.9 (*d*); 115.6 (*s*); 111.0 (*d*); 90.7 (*s*); 72.3 (*t*), 68.7 (*d*); 49.1 (*t*); 43.8 (*t*); 37.0 (*t*); 26.9 (*q*); 24.4 (*t*); 22.9 (*q*); 19.2 (*s*); 15.0 (*q*). ESI-MS: 872 ($[M+H]^+$).

(±)-{4-[2-(Ethylamino)ethoxy]-3,5-diiodophenyl}[2-(3-hydroxybutyl)benzofuran-3-yl]methanone Hydrochloride (**4**·HCl). To a soln. of **25** (56 mg, 0.064 mmol) in MeCN (10 ml) was added a 40% aq. HF soln. (57 µl, 1.280 mmol). The mixture was stirred for 2 h at r.t., then heated to 60° for 4 h, and stirred afterwards for 14 h at r.t. After adding brine (10 ml), the mixture was extracted with CH_2Cl_2 (3 × 20 ml), the combined org. phase was washed with brine (20 ml), dried ($MgSO_4$), and evaporated, and the residue was purified by FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 95:5:0.2): pure **4** (17 mg, 42%). Yellow oil. ^{1}H-NMR (300 MHz, CD_3OD): 8.20 (*s*, 2 H); 7.56 – 7.20 (*m*, 4 H); 4.23 (*t*, *J* = 5.5, 2 H); 3.78 – 3.64 (*m*, 1 H); 3.18 (*t*, *J* = 5.5, 2 H); 3.05 – 2.79 (*m*, 2 H); 2.82 (*q*, *J* = 7.2, 2 H); 1.93 – 1.83 (*m*, 2 H); 1.20 (*t*, *J* = 7.2, 3 H); 1.16 (*d*, *J* = 7.2, 3 H). ^{13}C-NMR (75 MHz,

CD_3OD; one signal missing): 187.3 (*s*); 167.2 (*s*); 162.5 (*s*); 155.1 (*s*); 141.9 (*d*); 139.7 (*s*); 127.5 (*s*); 126.0 (*d*); 124.9 (*d*); 122.0 (*d*); 112.1 (*d*); 91.5 (*s*); 72.8 (*t*), 67.7 (*d*); 49.8 (*t*); 44.5 (*t*); 37.7 (*t*); 25.9 (*t*); 23.3 (*q*); 14.6 (*q*).

The free base **4** in MeOH (10 ml) was transformed into its hydrochloride by adding 5 drops of 10% aq. HCl soln. The mixture was evaporated and then co-evaporated with MeOH (3×10 ml) to remove H_2O. The residue was dried under h.v. for 3 h: **4** · HCl (18 mg, 42%). White solid. M.p. 69.1 – 72.5°. IR ($CHCl_3$): 3430 (br.), 2960*s*, 2850*m*, 2700*s*, 2460*m*, 1655*m*, 1640*s*, 1590*m*, 1570*s*, 1555*s*, 1535*m*, 1470*m*, 1450*s*, 1430*s*, 1375*s*, 1320*m*, 1285*s*, 1240*s*, 1200*s*, 1185*m*, 1165*m*, 1120*m*, 1105*m*, 1070*m*, 1055*m*, 1015*s*, 960*m*, 940*s*, 935*m*, 905*w*, 840*w*, 820*w*, 700*w*, 660*w*. ^{1}H-NMR (500 MHz, CD_3OD): 8.23 (*s*, 2 H); 7.54 (*dd*, $J = 8.3, 0.7$, 1 H); 7.38 (*dd*, $J = 7.8, 0.6$, 1 H); 7.34 (*ddd*, $J = 8.3, 7.4, 1.3$, 1 H); 7.24 (*ddd*, $J = 7.8, 7.4, 0.9$, 1 H); 4.40 (*t*, $J = 5.0$, 2 H); 3.75 – 3.63 (*m*, 1 H); 3.65 (*t*, $J = 5.0$, 2 H); 3.33 – 3.28 (*m*, 2 H); 3.03 – 2.85 (*m*, 2 H); 1.94 – 1.82 (*m*, 2 H); 1.42 (*t*, $J = 7.3$, 3 H); 1.16 (*d*, $J = 6.2$, 3 H). ^{13}C-NMR (125 MHz, CD_3OD): 189.3 (*s*); 167.5 (*s*); 161.6 (*s*); 155.2 (*s*); 141.9 (*d*); 140.5 (*s*); 127.6 (*s*); 126.1 (*d*); 125.0 (*d*); 122.0 (*d*); 117.1 (*s*); 112.2 (*d*); 91.6 (*s*); 68.8 (*t*), 67.8 (*d*); 48.3 (*t*); 44.5 (*t*); 37.8 (*t*); 26.0 (*t*); 23.4 (*q*); 11.4 (*q*). ESI-MS: 634 ($[M + H]^+$).

(±)-[4-[2-(Diethylamino)ethoxy]-3,5-diiodophenyl][2-(3-hydroxybutyl)benzofuran-3-yl]methanone Hydrochloride (**3** · HCl). To a soln. of **23** (22 mg, 0.0245 mmol) in MeCN was added a 40% aq. HF soln. (22 µl, 0.489 mmol). The mixture was first stirred at r.t. for 14 h, then heated to 60° for 24 h. After quenching with H_2O (4 ml), CH_2Cl_2 (15 ml) was added, and the org. phase was separated. The aq. phase was adjusted to pH 10 with sat. $NaHCO_3$ soln. and extracted with CH_2Cl_2 (2×20 ml). The combined org. phase was washed with brine (10 ml), dried ($MgSO_4$), and evaporated. Pure **3** (6 mg, 37%) was obtained after FC (CH_2Cl_2/MeOH/25% aq. NH_3 soln. 95 : 5 : 0.2) as a yellow oil that was transformed into its hydrochloride by dissolving **3** in MeOH (4 ml) and adding 5 drops of 10% aq. HCl soln. After evaporation, the yellow residue was dried under h.v. for 4 h: **3** · HCl. ^{1}H-NMR (500 MHz, CD_3OD): 8.24 (*s*, 2 H); 7.55 (*d*, $J = 8.2$, 1 H); 7.39 (*d*, $J = 7.8$, 1 H); 7.35 (*ddd*, $J = 8.2, 7.3, 1.3$, 1 H); 7.25 (*ddd*, $J = 7.8, 7.6, 0.8$, 1 H); 4.46 (*t*, $J = 5.0$, 2 H); 3.84 (*t*, $J = 4.8$, 2 H); 3.74 – 3.67 (*m*, 1 H); 3.62 – 3.47 (*m*, 4 H); 3.03 – 2.88 (*m*, 2 H); 1.96 – 1.82 (*m*, 2 H); 1.46 (*t*, $J = 7.3$, 3 H); 1.17 (*d*, $J = 6.2$, 3 H). ^{13}C-NMR (125 MHz, CD_3OD, one signal missing): 189.2 (*s*); 167.5 (*s*); 161.8 (*s*); 155.2 (*s*); 141.9 (*d*); 140.5 (*s*); 127.6 (*s*); 126.1 (*d*); 125.0 (*d*); 122.0 (*d*); 117.1 (*s*); 111.9 (*d*); 91.7 (*s*); 67.8 (*d*); 67.6 (*t*); 52.4 (*t*); 37.8 (*t*); 26.0 (*t*); 23.8 (*q*); 9.2 (*q*). ESI-MS: 662 ($[M + H]^+$).

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