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This article is dedicated to Professor Satoshi Ōmura in celebration of his 2015 Nobel Prize.

Note

Novel 3,4,7-Substituted Benzofuran Derivatives Having Binding Affinity to κ-Opioid Receptor

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A series of novel 3,4,7-trisubstituted benzofuran derivatives were synthesized, and their binding affinity to κ- (KOR) and μ-opioid receptors (MOR) were evaluated. Several aryl ethers showed moderate binding activities to KOR (IC_{50}=3.9–11 μM) without binding to MOR.

Key words κ-opioid receptor; opioid; benzofuran; morphine

Morphine (**1**)[1] is the biological component of opium, which is obtained from the immature seedpod of poppy flowers (Fig. 1). When administered to patients, morphine causes a sense of euphoria and is a potent analgesic. The use of morphine to relieve pain is strictly controlled because of its high dependence-forming potential. Since the discovery of enkephalin (**6**)[2,3] and dynorphin (**7**)[4] from mammalian bodies, multiple morphine-like endogenous opioids were identified in rapid succession. Opioids exert their functions through one or more of three major receptor subtypes, defined as μ- (MOR), δ- (DOR), and κ-opioid receptors (KOR).[5–7] Portoghese and colleagues reported that MOR are primarily involved in forming dependence, while DOR and KOR participate in the action of analgesic effects with less risk for forming dependence. Therefore, selective ligands for DOR or KOR that do not interact with MOR are promising no-dependency therapeutic agents for pain and pruritus.[8,9] One example, the non-peptide selective KOR agonist nalfurafine (**4**),[10] was approved for treatment of pruritus in 2009.

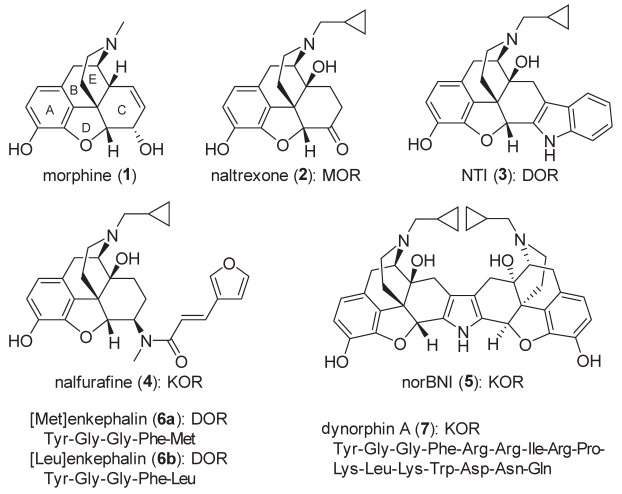

Fig. 1. Active Ligands for the μ- (MOR), δ- (DOR), and κ-Opioid Receptors (KOR)

The morphinan skeleton features a highly fused A–E ring system, where the B/E rings form a saturated azocine ring fused with the benzofuran moiety (A/D rings). Modification of the C-ring of the morphinan skeleton is important for the subtype selectivity. For example, naltrindole (NTI) (**3**)[11] and norbinaltorphimine (norBNI) (**5**),[12] each relatively large DOR- or KOR-selective antagonists, have an indole or pyrrole-fused C-ring, whereas the MOR selective ligand naltrexone (**2**)[13] has a cyclohexanone as the C-ring. Our group is thus involved in development of a novel synthetic route to morphine derivatives where the C-ring is constructed in a late synthetic stage, with the intent of identifying novel KOR-selective ligands (Chart 1). During the course of this research, we found that several synthetic intermediates before the C-ring formation showed moderate binding activities to KOR without binding to MOR. In this contribution, we report the synthesis and KOR binding affinity of our synthetic intermediates.

Synthesis of the 3,4,7-trisubstituted benzofuran derivatives **16**–**19** is shown in Chart 2. Benzofuran derivative **11**, bearing a methyl acetate moiety at the C3 position, was obtained by MOM protection of the hydroxy group of phenol **8**, *o*-lithiation–iodination, *O*-alkylation with methyl 4-bromocrotonate, followed by an intramolecular Heck reaction.[14] Reduction of the ester **11** using $LiAlH_4$ and protection with a *tert*-butyldimethylsilyl (TBS) group afforded silyl ether **12**. Addition of a Grignard reagent derived from **12** to 2-tetrahydropyranyl (THP)-protected (*S*)-glycidol **13** in the presence of CuI followed by a Mitsunobu reaction of the resulting alcohol with phthalimide gave benzofuran derivative **9**. After removal of the THP group, Swern oxidation followed by homologation using Ohira–Bestmann reagent[15,16] afforded alkyne **14**. After removal of phthalimide with 2-aminoethanol, reductive methylation and deprotection of the TBS group with tetrabutylam-

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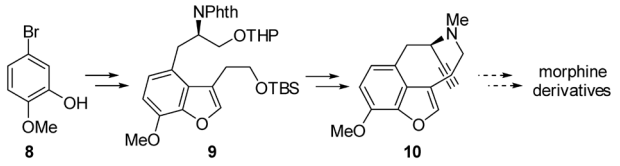
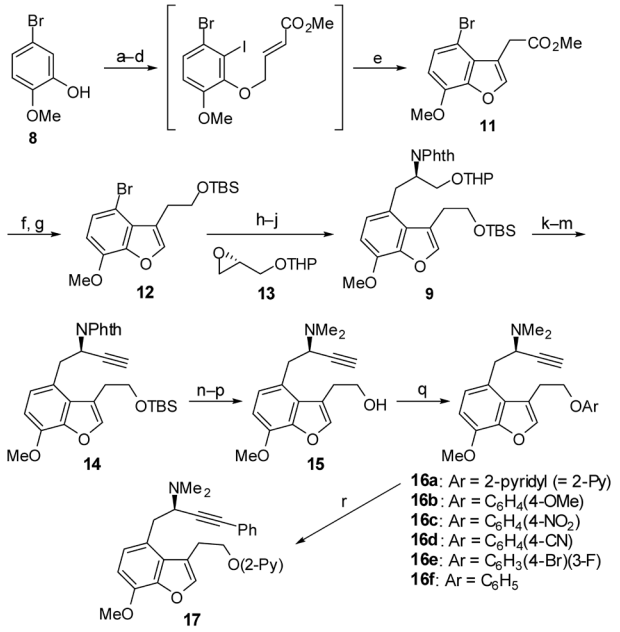


Chart 1. A Possible Synthetic Route to Morphine Derivatives



Reagents and conditions: (a) MOMCl, K_2CO_3, acetone, 70°C; (b) lithium diisopropyl amide (LDA) then I_2, THF, −78 to 0°C, (c) *p*-TsOH·H_2O, MeOH, 0°C; (d) methyl 4-bromocrotonate, K_2CO_3, DMF, 0°C; (e) $Pd(OAc)_2$, HCO_2Na, Na_2CO_3, $BnEt_3NCl$, DMF, 70°C, 34% in 5 steps; (f) $LiAlH_4$, THF, 0°C; (g) TBSCl, imidazole, DMF, 0°C, 84% in 2 steps; (h) Mg, THF, 65°C; (i) **13**, CuI, THF, 0°C; (j) phthalimide (=HNPhth), PPh_3, DEAD, THF, 0°C, 48% in 3 steps (based on epoxide **13**); (k) Me_2AlCl, CH_2Cl_2, −78°C; (l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0°C; (m) Ohira–Bestmann reagent, K_2CO_3, MeOH, 0°C, 54% in 3 steps; (n) 2-aminoethanol, toluene, 70°C; (o) HCHO aq., $NaBH(OAc)_3$, CH_3CN, r.t.; (p) TBAF, THF, r.t., 67% in 3 steps; (q) ArOH, PPh_3, bis(2-methoxyethyl) azodicarboxylate (DMEAD), THF, r.t., 32–63%; (r) iodobenzene, $PdCl_2(PPh_3)_2$ (2 mol%), CuI (2 mol%), Et_3N, THF, r.t., 13%.

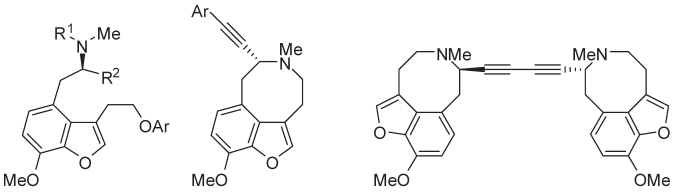
Chart 2. Synthesis of 3,4,7-Trisubstituted Benzofuran Derivatives

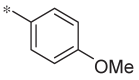
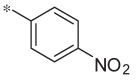
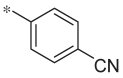
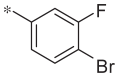
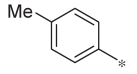
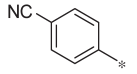
monium fluoride (TBAF) gave alcohol **15**. Finally, aryl ether formation under Mitsunobu conditions with various phenols gave **16a**–**f**. For comparison with internal alkyne, **16a** was converted to phenylethynyl-substituted derivative **17** using Sonogashira coupling. Other trisubstituted benzofurans **18** and **19** bearing a nosylamide or amino alcohol moiety (Table 1) were prepared in a similar manner (see Experimental).

Azocine-fused benzofuran derivatives **22a** and **b** were synthesized as follows (Chart 3): After phthalimide **9** was converted to nosylamide **20**, the eight-membered ring fused benzofuran **21** was obtained *via* deprotection of the TBS group with TBAF, cyclization by intramolecular Mitsunobu reaction, and removal of the THP group. After construction of a terminal alkyne, deprotection of the Ns group and reductive amination with formaldehyde gave alkyne **10**. Sonogashira cross-coupling reactions using iodobenzene derivatives having a *para*-substituent (Me or CN) afforded compounds **22a** and **b**. The dimeric compound **23**, produced during the Sonogashira coupling reaction, was also used for the biological evaluations considering the related dimeric structure of norBNI (**5**).

The results of the biological evaluations of the benzofuran derivatives are shown in Table 1. The biological activities

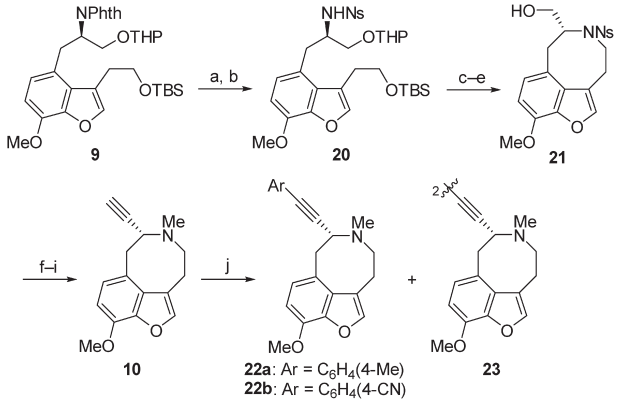
Table 1. Biological Activities of the Benzofuran Derivatives to MOR and KOR[a)]



Compound	R^1	R^2	Ar	IC_{50} (μM)	
				MOR	KOR
15	Me	C≡CH	H	—[b)]	>30
16a	Me	C≡CH		>30	4.9±2.1
16b	Me	C≡CH		>30	7.7±0.5
16c	Me	C≡CH		>30	3.9±1.5
16d	Me	C≡CH		>30	11±3.1
16e	Me	C≡CH		>30	9.7±2.2
17	Me	C≡CPh		>10	11±1.5
18	Ns	C≡CH		—[b)]	>30
19	Me	CH_2OH		>30	>30
22a				>30	>30
22b				>30	>30
23				>30	>30

a) Binding inhibition assays were performed using membranes from MOR- or KOR-expressing CHO cells. *b*) Not evaluated.

were evaluated as the inhibitory activities against [^{3}H]-diprenorphine binding to MOR and KOR. The tertiary amine derivatives **16a**–**e** possessing an ethynyl group showed moderate affinity to KOR (IC_{50}=3.9–11 μM), whereas all the tested compounds did not measurably bind to MOR. The alcohol **15** exhibited no KOR binding at 30 μM, suggesting that the aryl substituent on the hydroxy group is important for KOR binding. Interestingly, no significant difference in KOR inhibitory activities was observed among the aryl-modified derivatives **16a**–**e** having a basic pyridinyl group (IC_{50}=4.9 μM; **16a**), electron-donating anisyl group (IC_{50}=7.7 μM; **16b**), electron-withdrawing nitrophenyl (IC_{50}=3.9 μM; **16c**), cyanophenyl (IC_{50}=11 μM; **16d**) or dihalophenyl groups (IC_{50}=9.7 μM;



Reagents and conditions: (a) 2-aminoethanol, toluene, 70°C; (b) NsCl, diisopropylethylamine (DIPEA), CH_2Cl_2, r.t., 89% in 2 steps; (c) TBAF, THF, r.t.; (d) PPh_3, DMEAD, THF, r.t.; (e) PPTS, *i*-PrOH, 80°C, 68% in 3 steps; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0°C; (g) Ohira–Bestmann reagent, K_2CO_3, MeOH, 0°C; (h) thiophenol, K_2CO_3, CH_3CN, r.t.; (i) HCHO aq. $NaBH(OAc)_3$, CH_3CN, r.t., 55% in 4 steps; (j) Ar-I, $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), Et_3N, THF, r.t. (34% for **22a**; 27% for **22b**).

Chart 3. Synthesis of Azocine-Fused Benzofuran Derivatives

16e).[17] These results suggest that the presence of an aromatic substituent with a suitable size is more important for binding to KOR than polar interactions including hydrogen bonding. A phenyl group at the alkyne terminus is tolerated (IC_{50}=11 μM; **17**), which shows a possibility for further modification at this position. On the other hand, KOR binding activity disappeared with nosylamide **18** and alcohol **19** having a pyridyl group. Disappointingly, azocine-fused benzofurans **22a**,**b** and **23** showed no binding to KOR.

It should be noted that the alcohol **19** that inhibits neither KOR nor MOR has the characteristic substructure having a hydroxy group found in synthetic opioids including **2**–**5** (Fig. 1). Furthermore, the saturated azocine ring commonly present in many opioids apparently hinders binding of **22** to KOR. These results suggest that the binding mode and/or conformations of the potent derivatives **16** might be different from the well-known opioids.

In summary, we have identified novel 3,4,7-trisubstituted benzofuran derivatives that selectively bind to KOR but not MOR. Although the potency of these compounds is not sufficient for therapeutic uses, this study demonstrated that structurally simplified benzofuran derivatives can be considered as lead compounds for development of therapeutic agents for pain and pruritus with less drug dependence. Further studies to improve KOR binding activity, including removal of the methyl group on the phenolic hydroxy group and modifications of the alkyne terminus, are in progress in our laboratory.

Experimental

Chemistry Unless otherwise stated, reagents and anhydrous solvents (except for tetrahydrofuran (THF)) were used as purchased from commercial suppliers without further purification. THF was distilled from sodium benzophenone ketyl prior to use. Lithium diisopropylamide (LDA) solution was prepared at the time of use from diisopropylamine and *n*-BuLi solution (2.6 M in hexane). Glassware was dried at 65°C prior to use. IR spectra were determined on a JASCO FT/IR-4100 spectrometer. High resolution-mass spectra (HR-MS) were recorded on Shimadzu LC-ESI-IT-TOF-MS equipment. ^{1}H-NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$) as internal standard. ^{13}C-NMR spectra were recorded using a JEOL AL-500 and referenced to the residual solvent signal. Melting points (mp) were measured by a hot stage melting points apparatus (uncorrected). For flash chromatography, silica gel (Wakogel C-300E; Wako Pure Chemical Industries, Ltd., Osaka, Japan) or NH silica gel (Chromatorex NH-DM1020: Fuji Silysia Chemical Ltd., Japan) was employed.

Methyl 2-(4-Bromo-7-methoxybenzofuran-3-yl)acetate (11) This compound was prepared according to the reported procedure[14] with slight modifications: To a solution of the 5-bromo-2-methoxyphenol (**8**) (42.1 g, 201 mmol) in acetone (504 mL) were added K_2CO_3 (83.5 g, 604 mmol) and MOMCl (22.7 mL, 302 mmol) at room temperature (r.t.), and the mixture was stirred at 70°C for 1.5 h. The mixture was concentrated *in vacuo* and diluted with Et_2O. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue (24.5 g, *ca*. 99.0 mmol) was dissolved in THF (178 mL), and LDA (1.0 M in THF; 69.9 mL, 119 mmol) was added to the mixture at −78°C under the argon. After the mixture was stirred at the same temperature for 1.5 h, iodine (30.2 g, 119 mmol) in THF (248 mL) was added to the mixture. After the mixture was stirred at 0°C for 1.5 h, saturated $Na_2S_2O_3$ was added to the mixture, and the whole was extracted with Et_2O three times. The combined organic layer was washed with saturated $Na_2S_2O_3$, water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in MeOH (198 mL), and *p*-toluenesulfonic acid monohydrate (56.5 g, 297 mmol) was added to mixture at 0°C. After stirring at the same temperature for 1.5 h, the mixture was concentrated *in vacuo*. The residue was dissolved in Et_2O, and the organic layer was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was dissolved in *N*,*N*-dimethylformamide (DMF) (330 mL), and K_2CO_3 (20.6 g, 149 mmol) was added to the mixture at 0°C. After the mixture was stirred at the same temperature for 0.5 h, methyl 4-bromocrotonate (17.9 mL, 149 mmol) was added to the mixture. After stirring at the same temperature for 1.5 h, the mixture was poured into water, and the resulting solid was filtrated. The solid (22.2 g, 52.0 mmol) was dissolved in DMF (130 mL), and sodium formate (3.54 g, 52.0 mmol), sodium carbonate (13.8 g, 130 mmol), benzyltriethylammonium chloride (13.0 g, 57.2 mmol) and palladium acetate (584 mg, 2.60 mmol) was added to the mixture at r.t. under argon. After stirring at 70°C for 1 h, water was added to mixture and the whole was filtrated through celite and washed with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=10 : 1 to 3 : 1) to give **11** (9.93 g, 34% in 5 steps) as white solid: mp 145°C; IR (neat) 1725 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 3.94 (s, 2H), 3.98 (s, 3H), 6.67 (d, J=8.6 Hz, 1H), 7.26–7.28 (m, 1H), 7.64 (s, 1H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 29.0, 51.9, 56.1, 103.2, 108.4, 114.2, 127.0, 127.3, 144.5, 145.0, 145.6, 171.1; HR-MS [electrospray ionization (ESI)] Calcd for $C_{12}H_{11}BrNaO_4$ (MNa^+; ^{79}Br) 320.9733. Found 320.9738.

{2-(4-Bromo-7-methoxybenzofuran-3-yl)ethoxy}(*tert*-butyl)dimethylsilane (12) To a suspension of $LiAlH_4$ (1.90 g, 50.1 mmol) in dry THF (251 mL) was added a solution of **11**

(10.0 g, 33.4 mmol) in dry THF (167 mL) at 0°C. After the mixture was stirred at the same temperature for 10 min, saturated potassium sodium tartrate was added to the mixture at the same temperature. After stirring at r.t. for 16 h, the whole was extracted with EtOAc three times, and the combined organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. After the residue was dissolved in DMF (129 mL), imidazole (4.55 g, 66.8 mmol) and TBSCl (10.1 g, 66.8 mmol) were added to the mixture at 0°C. After the mixture was stirred at r.t. for 2 h, saturated NH_4Cl was added to the mixture, the whole was extracted with Et_2O twice, and the combined organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=10 : 1) to give **12** (10.8 g, 84% in 2 steps) as a colorless oil: IR (neat) 1247 (ArOMe), 1095 (ArOMe); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.02 (s, 6H), 0.88 (s, 9H), 3.10 (t, J=6.6 Hz, 2H), 3.93 (t, J=6.6 Hz, 2H), 3.98 (s, 3H), 6.65 (d, J=8.5 Hz, 1H), 7.26–7.29 (m, 1H), 7.51 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 5.3 (2C), 25.9 (3C), 27.5, 56.3, 56.4, 63.0, 104.5, 106.2, 107.2, 118.3, 126.8, 128.0, 143.7, 145.2; HR-MS (ESI) Calcd for $C_{17}H_{25}BrNaO_3$ (MNa^+; ^{79}Br) 407.0649. Found 407.0654.

2-{(2*R*)-1-[3-(2-{(*tert*-Butyldimethylsilyl)oxy}ethyl)-7-methoxybenzofuran-4-yl]-3-[(tetrahydro-2*H*-pyran-2-yl)-oxy]propan-2-yl}isoindoline-1,3-dione (9) Magnesium (440 mg, 18.1 mmol) was heated at 500°C for 2 h with vigorous stirring under reduced pressure. After cooling at room temperature, THF (5.00 mL), iodide (192 mg, 0.755 mmol) and 1,2-dibromoethane (65 μL, 0.755 mmol) were successively added under argon. After heating to 65°C, a solution of bromide **12** (5.80 g, 15.1 mmol) in THF (10.0 mL) was added to the mixture at the same temperature. After consumption of **12** (monitored by GC-MS analysis), the mixture was cooled to r.t. The concentration of the Grignard reagent was determined by titration with MeOH in the presence of 1,10-phenanthroline as indicator. To a solution of epoxide **13** (2.17 g, 13.7 mmol) in THF (122 mL) were added CuI (653 mg, 3.43 mmol) and the above Grignard reagent (1.0 M in THF; 15.1 mL, 15.1 mmol) at 0°C under argon. After stirring at the same temperature for 2 h, the mixture was quenched with saturated NH_4Cl and 5% NH_4OH, and the whole was extracted with EtOAc twice. The combined organic layer was washed with saturated NH_4Cl, water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The low-polar impurities present in the residue was removed by short column chromatography (silica gel; hexane–EtOAc=3 : 1). After the crude product (5.33 g, 11.5 mmol) was dissolved in THF (57.5 mL), phthalimide (5.08 g, 34.5 mmol), triphenylphosphine (9.05 g, 34.5 mmol) and diethyl azodicarboxylate (2.2 M in toluene; 15.7 mL, 34.5 mmol) were added to the mixture at 0°C. After stirring at the same temperature for 16 h, the mixture was filtrated through celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=10 : 1 to 1 : 1) to give **9** (3.89 g, 48%, 3 steps, based on epoxide **13**) as a mixture of diastereomers (*ca.* 1 : 1) derived from a THP ether moiety; pale yellow gummy solid: $[\alpha]_D^{28}$ +56.8 (c=0.450, $CHCl_3$); IR (neat) 2930 (ArH), 1709 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.01 (s, 6H), 0.86 (s, 9H), 1.35–1.62 (m, 6H), 3.08–3.12 (m, 2H), 3.37–3.41 (m, 1H), 3.50–3.63 (m, 3H), 3.79–3.81 (m, 1H), 3.89–3.92 (m, 3H), 3.94–3.97 (m, 2H), 4.08–4.11 (m, 0.5H), 4.24–4.27 (m, 0.5H), 4.57–4.62 (m, 1H), 4.76–4.79 (m, 1H), 6.54 (t, J=8.6 Hz, 1H), 6.81 (t, J=8.0 Hz, 1H), 7.49 (d, J=2.3 Hz, 1H), 7.67–7.69 (m, 2H), 7.75–7.79 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: −5.4 (2C), 18.2, 19.0, 19.1, 25.26, 25.34, 25.9 (3C), 26.0, 28.48, 28.51, 29.1, 30.3, 30.4, 31.4, 31.5, 52.2, 52.8, 55.9, 61.90, 61.92, 62.9, 63.0, 66.4, 66.6, 69.8, 80.9, 98.3, 98.8, 105.6, 106.7, 118.0, 123.09, 123.12, 123.2, 123.4, 123.5, 123.6, 123.9, 127.79, 127.81, 131.7, 131.8, 131.9, 133.8, 134.2, 134.3, 142.6, 142.7, 144.4, 144.88, 144.90, 167.9, 168.4, 168.5; HR-MS (ESI) Calcd for $C_{33}H_{43}NO_7SiNa$ (MNa^+) 616.2701. Found 616.2700.

(*R*)-2-[1-(3-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-7-methoxybenzofuran-4-yl)but-3-yn-2-yl]isoindoline-1,3-dione (14) To a solution of **9** (3.87 g, 6.52 mmol) in CH_2Cl_2 (53.0 mL) was added a solution of dimethyl aluminium chloride (1.09 M in hexane; 18.0 mL, 19.6 mmol) at –78°C under argon. After stirring at the same temperature for 1 h and at 0°C for further 1.5 h, saturated potassium sodium tartrate was added to the mixture, and the mixture was stirred at r.t. for 16 h. The whole was extracted with CH_2Cl_2 twice, the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of oxalyl chloride (1.12 mL, 13.0 mmol) in CH_2Cl_2 (7.2 mL) was added a DMSO (1.30 mL, 19.6 mmol) in CH_2Cl_2 (14.4 mL) at −78°C under argon. After the mixture was stirred at the same temperature for 1 h, the above crude alcohol (6.52 mmol) in CH_2Cl_2 (43.6 mL) was added to the mixture at the same temperature. After the mixture was stirred at the same temperature for 1.5 h, triethylamine (5.45 mL, 39.1 mmol) was added to the mixture. After 0.5 h at 0°C under stirring, saturated NH_4Cl was added to the mixture, and the whole was extracted with CH_2Cl_2 twice, the combined organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (65.2 mL), and K_2CO_3 (1.80 g, 13.0 mmol) and Ohira–Bestmann reagent (1.27 mL, 8.48 mmol) were added to the mixture at 0°C. After stirring at the same temperature for 3 h, the mixture was filtrated, and washed with methanol. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; hexane–EtOAc=10 : 1 to 2 : 1) to give **14** (1.79 g, 54% in 3 steps) as a pale yellow oil: $[\alpha]_D^{27}$ +26.2 (c=0.375, $CHCl_3$); IR (neat) 3274 (C≡CH), 2323 (C≡C), 1716 (C=O); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.01 (s, 6H), 0.86 (s, 9H), 2.33 (d, J=2.5 Hz, 1H), 3.07–3.16 (m, 2H), 3.56 (dd, J=13.7, 8.0 Hz, 1H), 3.78 (dd, J=13.7, 8.0 Hz, 1H), 3.93 (s, 3H), 3.96 (t, J=6.0 Hz, 2H), 5.28–5.32 (m, 1H), 6.61 (d, J=8.0 Hz, 1H), 6.94 (d, J=8.0 Hz, 1H), 7.52 (s, 1H), 7.71–7.74 (m, 2H), 7.81–7.84 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: −5.4 (2C), 18.2, 25.8 (3C), 28.5, 35.5, 42.8, 55.9, 62.9, 72.7, 79.6, 105.6, 117.9, 121.6, 123.5 (2C), 124.6 (2C), 128.0, 131.6 (2C), 134.1 (2C), 142.8, 144.8, 166.9 (2C); HR-MS (ESI) Calcd for $C_{29}H_{33}NO_5SiNa$ (MNa^+) 526.2020. Found 526.2021.

(*R*)-2-{4-[2-(Dimethylamino)but-3-yn-1-yl]-7-methoxybenzofuran-3-yl}ethan-1-ol (15) To a solution of **14** (1.77 g, 3.51 mmol) in toluene (35.0 mL) was added 2-aminoethanol (2.12 mL, 35.1 mmol) at r.t. After stirring at 70°C for 16 h, water was added to the mixture and the whole was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. After the residue was dissolved in acetonitrile (35.1 mL), formaldehyde (37% in water; 1.14 mL, 14.0 mmol) and $NaBH(OAc)_3$ (80%; 2.78 g, 10.5 mmol) were added to the

mixture at r.t. After the mixture was stirred at the same temperature for 16 h, saturated $NaHCO_3$ was added to the mixture and extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in THF (35.1 mL), and tetrabutylammonium fluoride (TBAF; 1.0 M in THF; 5.27 mL, 5.27 mmol) was added to the mixture at r.t. After 2 h under stirring, saturated NH_4Cl was added to the mixture, and the whole was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel, hexane–EtOAc=5 : 1 to 1 : 2) to give **15** (672 mg, 67% in 3 steps) as a colorless oil: $[\alpha]_D^{28}$ −39.0 (c=1.04, $CHCl_3$); IR (neat) 3273 (C≡CH), 3189 (OH), 2105 (C≡C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.85 (t, J=3.5 Hz, 1H), 2.28 (d, J=2.3 Hz, 1H), 2.33 (s, 6H), 3.03–3.12 (m, 3H), 3.26 (dd, J=13.2, 4.0 Hz, 1H), 3.60 (ddd, J=10.5, 4.5, 2.5 Hz, 1H), 3.83–3.89 (m, 1H), 3.92–3.96 (m, 1H), 3.98 (s, 3H), 6.74 (d, J=8.0 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 7.50 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.6, 36.8, 41.3 (2C), 55.9, 59.8, 62.4, 74.9, 79.5, 105.9, 117.3, 123.6, 124.8, 127.4, 142.5, 144.5, 145.1; HR-MS (ESI) Calcd for $C_{17}H_{22}NO_3$ (MH^+) 288.1594. Found 288.1593.

General Procedure for Synthesis of Aryl Ethers 16: Synthesis of (*R*)-1-{7-Methoxy-3-[2-(pyridin-2-yloxy)ethyl]-benzofuran-4-yl}-*N*,*N*-dimethylbut-3-yn-2-amine (16a) To a solution of **15** (25.0 mg, 0.0870 mmol) in THF (0.87 mL) were added 2-hydroxypyridine (24.8 mg, 0.261 mmol), triphenylphosphine (68.5 mg, 0.261 mmol) and bis(2-methoxyethyl) azodicarboxylate (DMEAD; 93%; 65.7 mg, 0.261 mmol) at r.t. After stirring at the same temperature for 16 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=5 : 1 to 1 : 1) to give **16a** (13.2 mg, 42%). Compounds **16b**–**f** were prepared using the corresponding phenols. Compound **16a**: white solid: mp 122–123°C; $[\alpha]_D^{28}$ −14.9 (c=0.525, $CHCl_3$); IR (neat) 3120 (C≡CH), 2952 (ArH), 2087 (C≡C), 1272 (ArOMe), 1016 (ArOMe); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.22 (d, J=2.3 Hz, 1H), 2.33 (s, 6H), 3.16–3.21 (m, 1H), 3.24–3.38 (m, 3H), 3.64 (ddd, J=10.0, 5.0, 2.0 Hz, 1H), 3.98 (s, 3H), 4.64 (t, J=6.6 Hz, 2H), 6.74 (d, J=8.0 Hz, 2H), 6.86 (dd, J=6.6, 5.4 Hz, 1H), 7.04 (d, J=8.0 Hz, 1H), 7.54–7.58 (m, 2H), 8.15 (dd, J=4.9, 2.0 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.0, 36.5, 41.5 (2C), 55.9, 59.9, 64.8, 74.7, 79.8, 105.8, 111.2, 116.8, 117.6, 123.9, 124.6, 127.7, 138.6, 142.3, 144.3, 144.9, 146.8, 163.5; HR-MS (FAB) Calcd for $C_{22}H_{25}N_2O_3$ (MH^+) 365.1860. Found 365.1861.

(*R*)-1-{7-Methoxy-3-[2-(4-methoxyphenoxy)ethyl]benzofuran-4-yl}-*N*,*N*-dimethylbut-3-yn-2-amine (16b) White gummy solid (yield: 57%): $[\alpha]_D^{28}$ −6.4 (c=0.345, $CHCl_3$); IR (neat) 3389 (C≡CH), 2931 (ArH), 2322 (C≡C), 1230 (ArOMe), 1041 (ArOMe); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.22 (d, J=1.7 Hz, 1H), 2.33 (s, 6H), 3.13–3.18 (m, 1H), 3.23 (dd, J=13.5, 4.9 Hz, 1H), 3.27–3.32 (m, 2H), 3.61–3.64 (m, 1H), 3.77 (s, 3H), 3.98 (s, 3H), 4.21–4.29 (m, 2H), 6.74 (d, J=8.0 Hz, 1H), 6.82–6.88 (m, 4H), 7.04 (d, J=8.0 Hz, 1H), 7.53 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.3, 36.5, 41.4 (2C), 55.7, 55.9, 59.8, 67.9, 74.7, 79.7, 105.9, 114.6 (2C), 115.6 (2C), 117.5, 123.7, 124.7, 127.7, 142.4, 144.4, 144.9, 152.7, 154.0; HR-MS (ESI) Calcd for $C_{24}H_{28}NO_4$ (MH^+) 394.2013. Found 394.2018.

(*R*)-1-{7-Methoxy-3-[2-(4-nitrophenoxy)ethyl]benzofuran-4-yl}-*N*,*N*-dimethylbut-3-yn-2-amine (16c) White solid (yield: 63%): mp 140°C; $[\alpha]_D^{28}$ −16.1 (c=1.12, $CHCl_3$); IR (neat) 3126 (C≡CH), 2938 (ArH), 2084 (C≡C), 1504 (NO_2), 1310 (NO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.24 (d, J=2.5 Hz, 1H), 2.33 (s, 6H), 3.16 (dd, J=13.2, 10.3 Hz, 1H), 3.23 (dd, J=13.2, 4.6 Hz, 1H), 3.32–3.42 (m, 2H), 3.61 (ddd, J=10.0, 4.0, 1.5 Hz, 1H), 3.99 (s, 3H), 4.34–4.42 (m, 2H), 6.76 (d, J=8.0 Hz, 1H), 6.97 (d, J=9.0 Hz, 2H), 7.07 (d, J=8.6 Hz, 1H), 7.52 (s, 1H), 8.20 (d, J=9.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.0, 36.7, 41.5 (2C), 55.9, 59.9, 68.1, 74.8, 79.6, 106.0, 114.5 (2C), 116.8, 123.6, 124.9, 125.9 (2C), 127.3, 141.6, 142.5, 144.5, 145.0, 163.6; HR-MS (ESI) Calcd for $C_{23}H_{25}N_2O_5$ (MH^+) 409.1758. Found 409.1759.

(*R*)-4-(2-{4-[2-(Dimethylamino)but-3-yn-1-yl]-7-methoxybenzofuran-3-yl}ethoxy)benzonitrile (16d) White solid (yield: 63%): mp 136°C; $[\alpha]_D^{28}$ −15.8 (c=0.760, $CHCl_3$); IR (neat) 3116 (C≡CH), 2953 (ArH), 2226 (C≡N), 2085 (C≡C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.24 (d, J=2.3 Hz, 1H), 2.32 (s, 6H), 3.15 (dd, J=13.5, 10.0 Hz, 1H), 3.22 (dd, J=13.5, 4.6 Hz, 1H), 3.30–3.40 (m, 2H), 3.61 (ddd, J=10.5, 4.5, 2.5 Hz, 1H), 3.98 (s, 3H), 4.29–4.37 (m, 2H), 6.76 (d, J=8.6 Hz, 1H), 6.95–6.98 (m, 2H), 7.06 (d, J=8.6 Hz, 1H), 7.51 (s, 1H), 7.57–7.60 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.9, 36.6, 41.5 (2C), 55.9, 59.9, 67.6, 74.8, 79.6, 104.2, 106.0, 115.2 (2C), 116.9, 119.1, 123.6, 124.9, 127.4, 134.0 (2C), 142.5, 144.5, 145.0, 161.9; HR-MS (ESI) Calcd for $C_{24}H_{25}N_2O_3$ (MH^+) 389.1860. Found 389.1858.

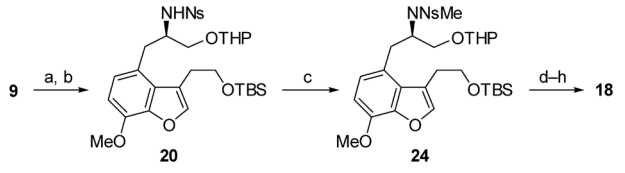
(*R*)-1-{3-[2-(4-Bromo-3-fluorophenoxy)ethyl]-7-methoxybenzofuran-4-yl}-*N*,*N*-dimethylbut-3-yn-2-amine (16e) White solid (yield: 60%): mp 142°C; $[\alpha]_D^{28}$ −15.3 (c=1.00, $CHCl_3$); IR (neat) 3118 (C≡CH), 2943 (ArH), 2088 (C≡C), 1167 (ArF); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.24 (d, J=1.7 Hz, 1H), 2.33 (s, 6H), 3.15 (dd, J=13.5, 10.0 Hz, 1H), 3.22 (dd, J=13.5, 4.6 Hz, 1H), 3.26–3.37 (m, 2H), 3.61 (ddd, J=10.0, 4.6, 1.7 Hz, 1H), 3.98 (s, 3H), 4.22–4.29 (m, 2H), 6.62 (dd, J=9.2, 2.9 Hz, 1H), 6.72 (dd, J=10.6, 2.9 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 7.40 (dd, J=10.6, 9.2 Hz, 1H), 7.50 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.0, 36.6, 41.4 (2C), 55.9, 59.9, 67.9, 74.8, 79.7, 103.4, 103.6, 106.0, 111.87, 111.89, 117.0, 123.6, 124.8, 127.4, 133.4, 142.4, 144.4, 144.9, 159.2; HR-MS (ESI) Calcd for $C_{23}H_{24}BrFNO_3$ (MH^+; ^{79}Br) 460.0919. Found 460.0920.

(*R*)-1-[7-Methoxy-3-(2-phenoxyethyl)benzofuran-4-yl]-*N*,*N*-dimethylbut-3-yn-2-amine (16f) White solid (yield: 32%): mp 114–115°C; $[\alpha]_D^{28}$ −17.8 (c=0.575, $CHCl_3$); IR (neat) 3257 (C≡CH), 2937 (ArH), 2088 (C≡C), 1243 (ArOMe), 1037 (ArOMe); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.23 (d, J=1.7 Hz, 1H), 2.33 (s, 6H), 3.16 (dd, J=13.5, 10.0 Hz, 1H), 3.24 (dd, J=14.0, 5.0 Hz, 1H), 3.30–3.38 (m, 2H), 3.63 (ddd, J=10.3, 4.5, 1.5 Hz, 1H), 3.98 (s, 3H), 4.26–4.34 (m, 2H), 6.74 (d, J=8.0 Hz, 1H), 6.92–6.97 (m, 3H), 7.05 (d, J=8.6 Hz, 1H), 7.27–7.30 (m, 2H), 7.54 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.3, 36.5, 41.4 (2C), 55.9, 59.9, 67.1, 74.8, 79.7, 105.9, 114.6 (2C), 117.5, 120.9, 123.7, 124.7, 127.7, 129.5 (2C), 142.5, 144.4, 144.9, 158.6; HR-MS (ESI) Calcd for $C_{23}H_{26}NO_3$ (MH^+) 364.1907. Found 364.1909.

(*R*)-1-{7-Methoxy-3-[2-(pyridin-2-yloxy)ethyl]benzofuran-4-yl}-*N*,*N*-dimethyl-4-phenylbut-3-yn-2-amine (17) To a solution of **16a** (30.0 mg, 0.0823 mmol) in Et_3N (1.20 mL) and THF (0.80 mL) were added iodobenzene (18 mL, 0.165 mmol), CuI (0.3 mg, 1.65 μmol) and $PdCl_2(PPh_3)_2$ (1.2 mg, 1.65 μmol; 2 mol%) at r.t. under argon. After stir-

ring at the same temperature for 2 h, the mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=5 : 1 to 1 : 1) to give **17** (4.6 mg, 13%) as a white gummy solid: $[\alpha]_D^{28}$ −80.8 (c=0.150, $CHCl_3$); IR (neat) 2931 (ArH), 2310 (C≡C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.41 (s, 6H), 3.30 (d, J=8.0 Hz, 2H), 3.37–3.39 (m, 2H), 3.83 (t, J=8.0 Hz, 1H), 3.98 (s, 3H), 4.62 (t, J=6.6 Hz, 2H), 6.72 (dd, J=8.0, 2.6 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H), 6.84–6.86 (m, 1H), 7.09 (d, J=8.0 Hz, 1H), 7.22–7.28 (m, 5H), 7.53–7.57 (m, 2H), 8.13 (dd, J=5.2, 1.1 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.2, 36.4, 41.8 (2C), 56.0, 60.9, 64.8, 85.9, 87.3, 106.0, 111.2, 116.9, 117.8, 123.2, 124.2, 124.8, 127.9, 128.0, 128.1 (2C), 131.6 (2C), 138.6, 142.3, 144.3, 144.9, 146.8, 163.6; HR-MS (ESI) Calcd for $C_{28}H_{29}N_2O_3$ (MH^+) 441.2173. Found 441.2175.

***N*-{(2*R*)-1-(3-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-7-methoxybenzofuran-4-yl)-3-[(tetrahydro-2*H*-pyran-2-yl)-oxy]propan-2-yl}-2-nitrobenzenesulfonamide (20) (Chart 4)** To a solution of **9** (1.12 g, 1.89 mmol) in toluene (18.9 mL) was added 2-aminoethanol (1.14 mL, 18.9 mmol) at r.t. After the mixture was stirred at 70°C for 16 h, water was added to the mixture and the whole was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. After the residue was dissolved in CH_2Cl_2 (18.9 mL), diisopropylethylamine (DIPEA; 495 μL, 2.84 mmol) and NsCl (439 mg, 1.98 mmol) were successively added to the mixture at r.t. After the mixture was stirred at the same temperature for 2 h, saturated $NaHCO_3$ was added to the mixture and the whole was extracted with CH_2Cl_2 twice. The combined organic layer was washed with brine, dried over $MaSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=5 : 1 to 1 : 1) to give **20** (1.09 g, 89%) as a mixture of diastereomers (*ca.* 1 : 1) derived from a THP ether moiety: yellow oil; $[\alpha]_D^{28}$ −45.4 (c=0.260, $CHCl_3$); IR (neat) 2934 (ArH), 1541 (NO_2), 1355 (NO_2), 1169 (SO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: −0.01 (s, 6H), 0.86 (s, 9H), 1.55–1.63 (m, 4H), 1.70–1.77 (m, 1H), 1.80–1.85 (m, 1H), 2.89–2.99 (m, 2.5H), 3.33–3.40 (m, 1.5H), 3.52–3.54 (m, 1H), 3.65–3.68 (m, 0.5H), 3.74–3.77 (m, 0.5H), 3.82–3.94 (m, 8H), 4.55–4.60 (m, 1H), 5.71–5.72 (m, 0.5H), 6.07–6.09 (m, 0.5H), 6.40–6.42 (m, 1H), 6.78–6.81 (m, 1H), 7.34–7.40 (m, 2H), 7.50–7.54 (m, 1H), 7.57–7.59 (m, 1H), 7.65–7.67 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: −5.5 (2C), 14.2, 18.2, 19.3, 19.7, 21.0, 25.2, 25.3, 25.8 (3C), 28.3, 28.4, 30.3, 30.6, 35.2, 35.2, 55.6, 56.95, 57.03, 60.38, 62.2, 62.75, 62.79, 70.01, 70.9, 99.3, 99.7, 105.2, 105.3, 118.0, 122.7, 122.8, 125.0, 125.29, 125.33, 127.4, 129.4, 129.5, 132.3, 134.3, 134.5, 142.27, 142.34, 144.2, 146.4; HR-MS (ESI) Calcd for $C_{31}H_{44}N_2NaO_{10}SSi$ (MNa^+) 671.2429. Found 671.2430.



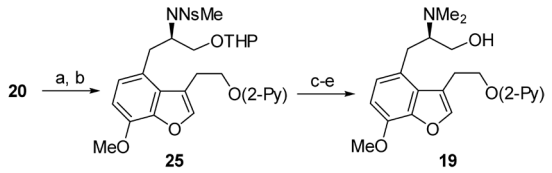
Reagents and conditions: (a) 2-aminoethanol, toluene, 70°C; (b) NsCl, DIPEA, CH_2Cl_2, r.t., 89% in 2 steps; (c) MeI, K_2CO_3, DMF, r.t., 84%; (d) Me_2AlCl, CH_2Cl_2, −78°C; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 to 0°C; (f) Ohira–Bestmann reagent, K_2CO_3, MeOH, 0°C; (g) TBAF, THF, r.t.; (h) pyridin-2-ol, PPh_3, DMEAD, THF, r.t., 25% in 5 steps.

Chart 4. Synthesis of Nosylamide **18**

***N*-{(2*R*)-1-(3-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-7-methoxybenzofuran-4-yl)-3-[(tetrahydro-2*H*-pyran-2-yl)-oxy]propan-2-yl}-*N*-methyl-2-nitrobenzenesulfonamide (24)** To a solution of **20** (900 mg, 1.39 mmol) in DMF (13.9 mL) were added K_2CO_3 (289 mg, 2.09 mmol) and MeI (104 μL, 1.69 mmol) at r.t. After the mixture was stirred at the same temperature for 16 h, water was added to the mixture and the whole was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=5 : 1 to 2 : 1) to give **24** (772 mg, 84%) as a mixture of diastereomers (*ca.* 1 : 1) derived from a THP ether moiety: yellow oil; $[\alpha]_D^{28}$ −60.3 (c=0.555, $CHCl_3$); IR (neat) 2950 (ArH), 1542 (NO_2), 1347 (NO_2), 1162 (SO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.10–0.12 (m, 6H), 0.88 (s, 9H), 1.52–1.75 (m, 6H), 2.90–3.07 (m, 3H), 3.15 (s, 3H), 3.32–3.36 (m, 0.5H), 3.44–3.53 (m, 2H), 3.57–3.60 (m, 0.5H), 3.78–3.82 (m, 1H), 3.89–3.93 (m, 5.5H), 3.98–4.01 (m, 0.5H), 4.25–4.32 (m, 1H), 4.58–4.61 (m, 1H), 6.40–6.44 (m, 1H), 6.82–6.86 (m, 1H), 7.20–7.23 (m, 1H), 7.40–7.43 (m, 1H), 7.45–7.50 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: −5.5 (2C), 13.2, 19.1, 19.2, 25.26, 25.28, 25.8 (3C), 28.27, 28.33, 29.7, 29.8, 30.26, 30.30, 31.5, 31.7, 55.7, 59.0, 59.1, 61.9, 62.1, 62.9, 68.13, 68.22, 98.7, 98.9, 105.19, 105.24, 118.06, 118.12, 122.70, 122.74, 123.6, 123.7, 124.9, 125.0, 127.3, 130.38, 130.42, 130.9, 132.19, 132.23, 133.4, 133.5, 142.2, 142.3, 144.06, 144.09, 144.26, 144.31, 146.9, 147.0; HR-MS (ESI) Calcd for $C_{32}H_{46}N_2O_9SSiNa$ (MNa^+) 685.2585. Found 685.2587.

***(R)*-*N*-[1-[7-Methoxy-3-{2-(pyridin-2-yloxy)ethyl}benzofuran-4-yl]but-3-yn-2-yl]-*N*-methyl-2-nitrobenzenesulfonamide (18)** By the similar procedures for the synthesis of **16** from compound **9**, the compound **18** was obtained as pale yellow gummy solid (yield: 25% in 5 steps): $[\alpha]_D^{26}$ −34.4 (c=0.490, $CHCl_3$); IR (neat) 3279 (C≡CH), 2927 (ArH), 2113 (C≡C), 1543 (NO_2), 1349 (NO_2), 1165 (SO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.25 (d, J=2.3 Hz, 1H), 3.10 (s, 3H), 3.23–3.36 (m, 3H), 3.44 (dd, J=14.7, 8.0 Hz, 1H), 3.94 (s, 3H), 4.59–4.68 (m, 2H), 4.98 (ddd, J=8.0, 8.0, 2.0 Hz, 1H), 6.62 (d, J=8.0 Hz, 1H), 6.75 (d, J=8.0 Hz, 1H), 6.87 (dd, J=6.9, 5.2 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.43–7.47 (m, 1H), 7.53–7.60 (m, 4H), 7.75 (dd, J=8.0, 1.1 Hz, 1H), 8.16 (dd, J=4.9, 1.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 24.9, 30.2, 36.3, 52.2, 55.8, 64.8, 75.1, 79.1, 105.7, 111.1, 116.9, 117.4, 121.0, 124.1, 125.4, 127.6, 130.5, 131.3, 132.2, 133.2, 138.7, 142.46, 142.47, 144.7, 146.9, 147.8, 163.4; HR-MS (ESI) Calcd for $C_{27}H_{25}N_3O_7SNa$ (MNa^+) 558.1305. Found 558.1306.

***N*-{[(2*R*)-1-{7-Methoxy-3-[2-(pyridin-2-yloxy)ethyl]benzofuran-4-yl}-3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propan-2-yl]-*N*-methy}-2-nitrobenzenesulfonamide (25) (Chart 5)** Pale yellow gummy solid (yield 40% in two steps; mixture of diastereomers (*ca.* 1 : 1) derived from a THP ether moiety): $[\alpha]_D^{28}$ −30.2 (c=0.465, $CHCl_3$); IR (neat) 2922 (ArH), 1543 (NO_2), 1363 (NO_2), 1160 (SO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.48–1.77 (m, 6H), 2.91–3.03 (m, 1H), 3.15 (s, 3H), 3.26–3.43 (m, 2.5H), 3.48–3.54 (m, 2H), 3.58–3.61 (m, 0.5H), 3.73–3.85 (m, 1H), 3.88 (s, 3H), 3.91–3.96 (m, 0.5H), 3.98–4.02 (m, 0.5H), 4.25–4.33 (m, 1H), 4.56–4.66 (m, 3H), 6.40–6.43 (m, 1H), 6.73–6.75 (m, 1H), 6.84–6.89 (m, 2H), 7.16–7.20 (m, 1H), 7.38–7.51 (m, 4H), 7.55–7.59 (m, 1H), 8.15–8.17 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 19.1, 19.3, 24.8, 24.9, 25.2, 25.3,



Reagents and conditions: (a) TBAF, THF, r.t.; (b) pyridin-2-ol, PPh_3, DMEAD, THF, r.t., 40% in 2 steps; (c) thiophenol, K_2CO_3, CH_3CN, r.t.; (d) HCHO aq., $NaBH(OAc)_3$, CH_3CN, r.t.; (e) pyridinium *p*-toluenesulfonate, EtOH, r.t., 79% in 3 steps.

Chart 5. Synthesis of Alcohol **19**

29.75. 29.81, 30.26, 30.28, 31.5, 31.7, 55.7, 59.06, 59.14, 61.9, 62.2, 64.9, 65.0, 68.2, 68.4, 98.8, 99.0, 105.38, 105.45, 111.10, 111.13, 116.9, 117.6, 122.7, 122.8, 123.7, 123.8, 125.17, 125.21, 130.48, 130.53, 130.92, 130.94, 132.2, 133.4, 133.6, 138.7, 141.9, 142.1, 144.12, 144.14, 144.4, 146.7, 146.9, 163.5; HR-MS (ESI) Calcd for $C_{31}H_{36}N_3O_9$ (MH^+) 626.2167. Found 626.2169.

(*R*)-2-(Dimethylamino)-3-{7-methoxy-3-[2-(pyridin-2-yloxy)ethyl]benzofuran-4-yl}propan-1-ol (19) To a solution of **25** (55.0 mg, 0.0879 mmol) in acetonitrile (0.900 mL) were added K_2CO_3 (121 mg, 0.879 mmol) and thiophenol (45 μL, 0.440 mmol) at r.t. After the mixture was stirred at the same temperature for 2 h, saturated $NaHCO_3$ was added to the mixture, and the whole was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The remaining thiophenol in the residue was removed by short column chromatography (silica gel; $CHCl_3$ to $CHCl_3$–MeOH=10 : 1) to afford the corresponding amine (36.6 mg) as crude product. To this amine (15.0 mg, *ca*. 0.0340 mmol) in acetonitrile (0.400 mL) were added formaldehyde (6.0 μL, 0.0680 mmol) and sodium triacetoxyborohydride (14.0 mg, 0.0510 mmol) at r.t. After the mixture was stirred at the same temperature for 16 h, saturated $NaHCO_3$ was added to the mixture, and the mixture was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. After the residue dissolved in EtOH (330 μL), pyridinium *p*-toluenesulfonate (1.2 mg, 4.95 μmol) was added to the mixture at r.t. After stirring at the same temperature for 2 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=5 : 1 to 1 : 1) to give **19** (10.1 mg, 79%) as a white gummy solid: $[\alpha]_D^{28}$ −10.5 (c=0.425, $CHCl_3$); IR (neat) 2923 (OH), 1273 (ArOMe), 1013 (ArOMe); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.39 (s, 6H), 2.70 (dd, J=13.7, 10.3 Hz, 1H), 2.96–3.02 (m, 1H), 3.23–3.37 (m, 5H), 3.98 (s, 3H), 4.62 (t, J=6.9 Hz, 2H), 6.71 (d, J=8.0 Hz, 1H), 6.74 (d, J=8.6 Hz, 1H), 6.86–6.89 (m, 2H), 7.54 (s, 1H), 7.56–7.59 (m, 1H), 8.15 (dd, J=5.4, 1.4 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.3, 26.8, 40.2 (2C), 56.0, 60.3, 64.8, 66.0, 106.0, 111.2, 116.9, 117.3, 124.3, 124.5, 127.5, 138.7, 142.4, 144.2, 145.0, 146.8, 163.4; HR-MS (ESI) Calcd for $C_{21}H_{27}N_2O_4$ (MH^+) 371.1965. Found 371.1967.

(*R*)-{3-Methoxy-8-[(2-nitrophenyl)sulfonyl]-7,8,9,10-tetrahydro-6*H*-benzofuro[3,4-*de*]azocin-7-yl}methanol (21) To a stirred solution of **20** (2.58 g, 3.98 mmol) in THF (19.9 mL) was added TBAF (1.0 M in THF; 19.9 mL, 19.9 mmol) at r.t. After stirring at the same temperature for 2 h, saturated $NaHCO_3$ was added to the mixture and the whole was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. After the residue was dissolved in THF (39.8 mL), triphenylphosphine (3.12 mg, 11.9 mmol) and DMEAD (2.79 mg, 11.9 mmol) were added to the mixture at r.t. After stirring at the same temperature for 1.5 h, saturated $NaHCO_3$ was added to the mixture and the whole was extracted with EtOAc twice. The combined organic layer was washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. After the residue was dissolved in *i*-PrOH (39.8 mL), pyridinium *p*-toluenesulfonate (150 mg, 0.597 mmol) was added to the mixture at r.t. After stirring at 80°C for 2 h, Et_3N (166 μL, 1.19 mmol) was added to the mixture and the whole was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexane–EtOAc=3 : 1 to 1 : 2) to give **21** (1.17 g, 68% in 3 steps) as a colorless oil: $[\alpha]_D^{28}$ +27.2 (c=0.370, $CHCl_3$); IR (neat) 2927 (OH), 1541 (NO_2), 1373 (NO_2), 1162 (SO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.97 (t, J=5.7 Hz, 1H), 2.85 (dd, J=13.7, 5.2 Hz, 1H), 2.96 (dd, J=14.9, 7.4 Hz, 1H), 3.13–3.24 (m, 2H), 3.73 (dd, J=14.9, 6.9 Hz, 1H), 3.90 (t, J=6.3 Hz, 2H), 3.94 (s, 3H), 4.28–4.35 (m, 1H), 4.53–4.57 (m, 1H), 6.56 (d, J=7.4 Hz, 1H), 6.87 (d, J=8.0 Hz, 1H), 7.01 (d, J=7.4 Hz, 1H), 7.17 (d, J=7.4 Hz, 1H), 7.22 (d, J=7.4 Hz, 1H), 7.26–7.27 (m, 1H), 7.42 (d, J=7.4 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 23.2, 32.9, 42.8, 55.8, 60.1, 62.5, 105.9, 117.3, 122.6, 122.7, 123.8, 128.7, 129.8, 130.5, 132.4, 133.0, 141.2, 143.8, 144.3, 147.2; HR-MS (ESI) Calcd for $C_{20}H_{20}N_2O_7SK$ (MK^+) 471.0623. Found 471.0623.

(*R*)-7-Ethynyl-3-methoxy-8-methyl-7,8,9,10-tetrahydro-6*H*-benzofuro[3,4-*de*]azocine (10) By a procedure similar to that described for synthesis of **14** from **9**, the alcohol **21** (510 mg, 1.18 mmol) was converted to the corresponding alkyne (338 mg) as a crude product (Me_2AlCl treatment was not applied). To this alkyne (150 mg, 0.352 mmol) in DMF (3.5 mL) were added K_2CO_3 (147 mg, 1.06 mmol) and thiophenol (90 μL, 0.880 mmol) at 0°C. After the mixture was stirred at the same temperature for 1 h, saturated $NaHCO_3$ was added to the mixture, and the whole was extracted with EtOAc three times. The combined organic layer was washed with 1 N NaOH, water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The remaining thiophenol in the residue was removed by short column chromatography (silica gel; $CHCl_3$ to $CHCl_3$–MeOH=10 : 1) to afford the corresponding amine (82.9 mg) as crude product. To this amine (82.0 mg, 0.340 mmol) in acetonitrile (3.40 mL) were added formaldehyde (37%; 57 μL, 0.680 mmol) and sodium triacetoxyborohydride (135 mg, 0.510 mmol) at r.t. After stirring at the same temperature for 3 h, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (NH-silica gel, hexane/EtOAc=10/1 to 2/1) to give **10** (75.5 mg, 55% in 4 steps) as a white solid: mp 112°C; $[\alpha]_D^{28}$ +32.7 (c=0.980, $CHCl_3$); IR (neat) 3257 (C≡CH), 2097 (C≡C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.26 (s, 3H), 2.42 (s, 1H), 2.53–2.59 (m, 1H), 2.74–2.80 (m, 1H), 3.00 (dd, J=14.3, 5.7 Hz, 1H), 3.10–3.20 (m, 2H), 3.54 (dd, J=14.0, 12.5 Hz, 1H), 3.64–3.67 (m, 1H), 3.97 (s, 3H), 6.66 (d, J=8.0 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H), 7.35 (d, J=1.1 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 23.6, 38.4, 47.0, 52.3, 55.9, 57.6, 73.4, 81.0, 105.6, 119.8, 122.6, 123.8, 132.2, 140.1, 143.6, 144.6; HR-MS (ESI) Calcd for $C_{16}H_{18}NO_2$ (MH^+) 256.1332. Found 256.1337.

(*R*)-3-Methoxy-8-methyl-7-(*p*-tolylethynyl)-7,8,9,10-tetrahydro-6*H*-benzofuro[3,4-*de*]azocine (22a) and 1,4-Bis[(*R*)-3-methoxy-8-methyl-7,8,9,10-tetrahydro-6*H*-

benzofuro[3,4-*de*]azocin-7-yl]buta-1,3-diyne (23) To a solution of 1-iodo-4-methylbenzene (17.1 mg, 0.0784 mmol) in THF (0.400 mL) and Et_3N (0.400 mL) were added CuI (0.4 mg, 1.96 μmol) and $PdCl_2(PPh_3)_2$ (1.4 mg, 1.96 μmol) at r.t. under argon. To the mixture was added **10** (10.0 mg, 0.0392 mmol) at the same temperature. After stirring for 2 h, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; hexane–EtOAc=5 : 1 to 1 : 1) to give **22a** (4.6 mg, 34%) and **23** (5.5 mg, 55%).

Compound **22a**

Pale red solid; mp 127–128°C; $[\alpha]_D^{28}$ +32.7 (c=0.980, $CHCl_3$); IR (neat) 2933 (ArH), 2324 (C≡C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 2.36 (s, 3H), 2.57–2.61 (m, 1H), 2.78 (dd, J=14.9, 6.9 Hz, 1H), 3.07–3.08 (m, 1H), 3.15–3.22 (m, 1H), 3.28 (dd, J=12.0, 6.9 Hz, 1H), 3.61 (dd, J=14.0, 13.5 Hz, 1H), 3.83–3.86 (m, 1H), 3.98 (s, 3H), 6.67 (d, J=7.4 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 7.14 (d, J=8.0 Hz, 2H), 7.36 (d, J=1.1 Hz, 1H), 7.38–7.40 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 21.5, 23.7, 38.6, 47.3, 52.5, 56.0 (2C), 58.4, 86.1, 105.7, 120.0, 120.1, 122.6, 124.1, 129.0 (2C), 131.7 (2C), 131.9, 138.1, 140.1, 143.6, 144.5; HR-MS (ESI) Calcd for $C_{23}H_{24}NO_2$ (MH^+) 346.1802. Found 346.1804.

Compound **23**

Pale red solid; mp 156°C; IR (neat) 2936 (ArH), 2327 (C≡C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 6H), 2.57–2.63 (m, 2H), 2.79 (dd, J=14.9, 7.4 Hz, 2H), 3.01 (dd, J=14.9, 6.0 Hz, 2H), 3.14–3.20 (m, 2H), 3.25 (dd, J=12.6, 6.9 Hz, 2H), 3.58 (dd, J=14.0, 12.5 Hz, 2H), 3.75 (dd, J=12.6, 5.7 Hz, 2H), 3.97 (s, 6H), 6.66 (d, J=8.0 Hz, 2H), 6.84 (d, J=8.0 Hz, 2H), 7.36 (d, J=1.1 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 23.6 (2C), 38.1 (2C), 47.2 (2C), 52.5 (2C), 56.0 (2C), 58.4 (2C), 70.1 (2C), 105.7 (4C), 119.7 (2C), 122.6 (2C), 123.4 (2C), 140.2 (4C), 143.6 (2C), 144.6 (2C); HR-MS (ESI) Calcd for $C_{32}H_{33}N_2O_4$ (MH^+) 509.2435. Found 509.2434.

(*R*)-4-[(3-Methoxy-8-methyl-7,8,9,10-tetrahydro-6*H*-benzofuro[3,4-*de*]azocin-7-yl)ethynyl]benzonitrile (22b) By a procedure similar to that described for the synthesis of **22a**, **10** (30.0 mg, 0.117 mmol) was converted to **22b** (11.1 mg, 27%) and **23** (5.2 mg, 17%) using 4-iodobenzonitrile.

Compound **22b**

White solid; mp 119°C; $[\alpha]_D^{28}$ +0.935 (c=0.550, $CHCl_3$); IR (neat) 2933 (ArH), 2334 (C≡C), 2219 (C≡N); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.33 (s, 3H), 2.61–2.65 (m, 1H), 2.80 (dd, J=14.6, 7.2 Hz, 1H), 3.08–3.09 (m, 1H), 3.14–3.26 (m, 2H), 3.61 (dd, J=13.5, 13.0 Hz, 1H), 3.83–3.92 (m, 1H), 3.98 (s, 3H), 6.68 (d, J=7.4 Hz, 1H), 6.87 (d, J=8.0 Hz, 1H), 7.37 (s, 1H), 7.57–7.63 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 23.7, 38.2, 47.2, 52.5, 56.0, 58.4, 84.9, 92.0, 105.7, 111.3, 118.5, 119.7, 122.7, 123.5, 128.1, 131.8, 132.0 (2C), 132.3 (2C), 140.2, 143.6, 144.6; HR-MS (ESI) Calcd for $C_{23}H_{21}N_2O_2$ (MH^+) 357.1598. Found 357.1597.

Evaluation of MOR and KOR Binding Inhibition Binding inhibition assays were performed by the similar protocols as described previously.[18] Membranes from MOR- or KOR-expressing CHO cells were incubated with 50 μL of compound solution, 25 μL of radioactive ligand [[15,16-^{3}H]-diprenorphne, 0.4 nM, PerkinElmer, Inc. Life Sciences] solution, and 25 μL of membrane solution in assay buffer [50 mM *N*-(2-hydroxyethyl)-piperazine-*N*′-2-ethanesulfonic acid (HEPES) (pH 7.4), 5 mM $MgCl_2$, 1 mM $CaCl_2$, 0.1% bovine serum albumin (BSA)]. Reaction mixtures were filtered through GF/B filters, pretreated with 0.3% polyethyleneimine. Filters were washed with [50 mM HEPES (pH 7.4), 500 mM NaCl, 0.1% BSA] and dried at 55°C. Bound radioactivity was measured by TopCount (PerkinElmer, Inc. Life Sciences) in the presence of MicroScint-O (30 μL) (PerkinElmer, Inc. Life Sciences). PF-4455242[19] (IC_{50}=0.28±0.11 μM for KOR) and [Met]enkephalin (**6a**) (IC_{50}=0.29±0.07 μM for MOR) were used as positive controls.

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Conflict of Interest The authors declare no conflict of interest.

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