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PAPER

Stereoselective synthesis of novel pyrazole derivatives using *tert*-butansulfonamide as a chiral auxiliary†

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A novel chiral pyrazole derivative was developed by our research program as a potent PDE4 inhibitor for the treatment of anti-inflammatory diseases, such as asthma and chronic obstructive pulmonary disease. The asymmetric synthesis of the inhibitors carrying the pyrazole moiety, including nitrogen directly bonded to a chiral center, through a novel approach is disclosed. The key steps of the synthetic sequence begin with the preparation of chiral toluenesulfinyl imine by the condensation of (*R*)- and (*S*)-*tert*-butanesulfinamide with an aldehyde. Next, a corresponding chiral amine synthesis by a stereoselective addition reaction of 4-picolyl lithium to the chiral toluenesulfinyl imine is performed, followed by desulfination. The preparation of the *cis*-type enaminone from the addition of the enaminone to the corresponding chiral amine is then accomplished, with further transformation into the pyrazole derivatives through the amination of the enaminones and subsequent dehydro-cyclization. A total of 8 steps are completed to produce a 5.5% yield (100% ee).

1. Introduction

Phosphodiesterase (PDE), a member of the cyclic nucleotide phosphodiesterase family, is responsible for the hydrolysis of cAMP and cGMP. Within the diverse group of PDE isozymes, PDE4 is a cAMP-specific isoenzyme. cAMP is an important intracellular secondary messenger in cellular functions that relays the signals from hormones at specific cell-surface receptors.[1] An increase in cAMP due to the stimulation of adenylyl cyclase or the inhibition of PDEs affects the activity of the immune system and inflammatory cells.[2] Therefore, PDE4 has received considerable attention as a new drug target for the treatment of inflammatory diseases, such as asthma and chronic obstructive pulmonary disease.[3]

During our research program for the development of PDE4 inhibitors,[4] compound **1** was identified as a potent PDE4 inhibitor (IC_{50} = 0.5 nM, Fig. 1).[5] The enantiomers of **1** could be separated by preparative chiral HPLC,[6] and the IC_{50} values toward PDE4 inhibition were evaluated as 5 nM (**1*R***) and 0.5 nM (**1*S***). To obtain large amounts of the enantiomers for an *in vivo* study in an asthma animal model, we developed an asymmetrical synthetic method for **1*R*** and **1*S*** through a route that included the preparation of the corresponding chiral amines using (*R*)- and (*S*)-*tert*-butanesulfinamide as a chiral auxiliary[7] followed by *cis*-type enamine synthesis of the amines. Further transformations were performed to give the pyrazole derivatives through the amination of the enamines and subsequent dehydro-cyclization. We report the synthetic procedure of racemic **1** and the asymmetric synthesis of chiral pyrazoles **1*R*** and **1*S***.[8]

2. Results and discussion

2.1. Synthesis of racemic 1

Synthesis of racemic compound **1** was achieved *via* Michael addition of the pyrazole anion to enone **3** using conventional synthetic procedures, as shown in Scheme 1. Compound **2** was prepared from 3,4-dihydroxybenzaldehyde, as reported in the literature.[9] Michael adduct **3** was obtained by the condensation of **2** and pyridine-4-yl acetic acid ethyl ester with $CH_3CO_2NH_4$ by refluxing in acetic acid for 2 days. Because the Michael addition

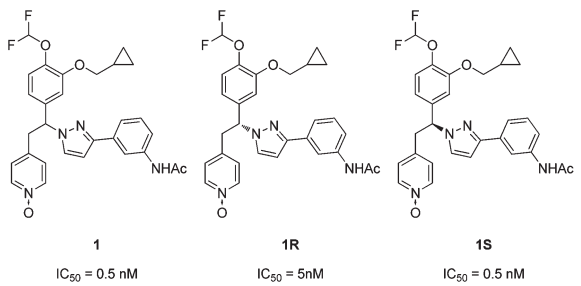

Fig. 1 PDE4 inhibitor structures for **1**, **1*R*** and **1*S***.

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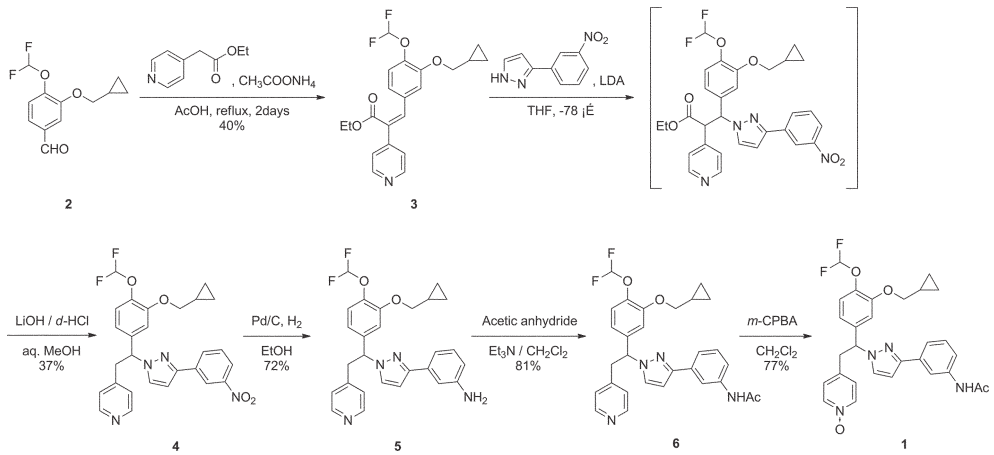


Scheme 1 Synthesis of racemic **1**.

reaction of the pyrazole anion has not been previously reported in the literature, diverse reaction conditions, including such bases as LDA, triethylamine, NaH, K_2CO_3, and Cs_2CO_3, were attempted. Only the reaction with LDA afforded the desired product. Although this reaction proceeded non-stereoselectively, and the products formed as nearly 1 : 1 *cis* : *trans* isomers, the isomeric mixture was not separated. The products were hydrolyzed *in situ* using LiOH in MeOH–H_2O mixed solvent at room temperature, and the subsequent decarboxylation of the carboxylic acid proceeded using dilute hydrogen chloride water solution to give **4** in two steps with a 37% yield.

The reduction of the nitro group in **4** by a hydrogenation reaction using palladium catalyst was performed to give **5** with a yield of 72%. This reaction was followed by acylation of the amino group using acetic anhydride to give **6** with an 81% yield. Compound **1** was obtained in 77% yield by the oxidation of the pyridine moiety of **1** with *m*-CPBA. Compound **1** represents the potent PDE4 inhibitor (PDE4, IC_{50} = 0.5 nM).

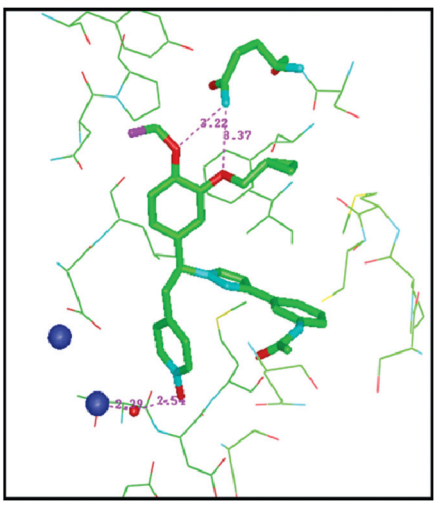


Fig. 2 X-ray co-crystal structure of **1*S*** and the PDE4 enzyme.

2.2. Synthesis of chiral 1*S* and 1*R*

1*R* and **1*S***, which are enantiomers of **1**, were separated by chiral prep-HPLC, and the inhibitory activities were determined, showing that **1*S*** (IC_{50} = 0.5 nM) is more active than **1*R*** (IC_{50} = 5 nM) against the PDE4 enzyme. The absolute configurations of these compounds were elucidated by the 1 : 1 X-ray co-crystal structure of **1*S*** and the PDE4 enzyme (Fig. 2; PDB ID code: 3V9B). In this structure, the pyridine-*N*-oxide of **1*S*** interacted with Mg, mediated by water, present in the PDE4 enzyme. Moreover, the pyridine-*N*-oxide of **1*R*** was slightly more distant than that of **1*S***, as determined from the calculation model.[10] Therefore, the inhibitory activity of **1*R*** is probably weaker than that of **1*S***.

To obtain large amounts of the enantiomers for an *in vivo* study, we developed the asymmetrical synthesis of **1*R*** and **1*S***. A novel synthetic procedure for the enantiomers (**1*R***, **1*S***) needed to be designed because the preparation of these compounds using the synthetic method for racemic compound **1** would be difficult. The structures of **1*R*** and **1*S*** contain the pyrazole moiety directly bonded to a chiral center.[11] The synthesis of this type of compound has not been previously reported. Using retrosynthetic analysis (Fig. 3), the pyrazole derivative was obtained from *N*-amination of the *cis*-type enaminone derived from the addition of the enamine to the corresponding chiral amine, generated from the addition reaction of 4-picolyl lithium to a chiral sulfinimine, which could be prepared by the condensation of the chiral sulfonamide with 3-nitrobenzaldehyde. First, the (*R*)-*N*-*p*-toluenesulfinyl group was selected as a chiral auxiliary to prepare (*R*)-*N*-*p*-toluenesulfinyl imine (**7**) by condensation with aldehyde **2**. This reaction led to chiral sulfonamide **8** by the reaction of 4-picolyl lithium with **7**, as shown in Scheme 2.[12] (*R*)-*N*-*p*-Toluenesulfinyl imine (**7**) was synthesized through the reaction of menthyl *p*-toluenesulfinate with LiHMDS to give (*R*)-*N*-*p*-toluenesulfinamide; the subsequent dehydration reaction of this sulfinamide with aldehyde **2** is a known procedure. When 4-picolyl lithium reacted with imine **7** at −78 °C in THF, chiral sulfonamide **8a** was yielded preferentially to **8b** with good selectivity (60% yield, 80% de). The diastereoselectivity of this reaction was not consistent with the closed transition state. However, an anti-Ellman's model that suggests rapid *E*/*Z* isomerization of the imine has been proposed in which the coordination of lithium ion to the catechol part of substrate **8a**

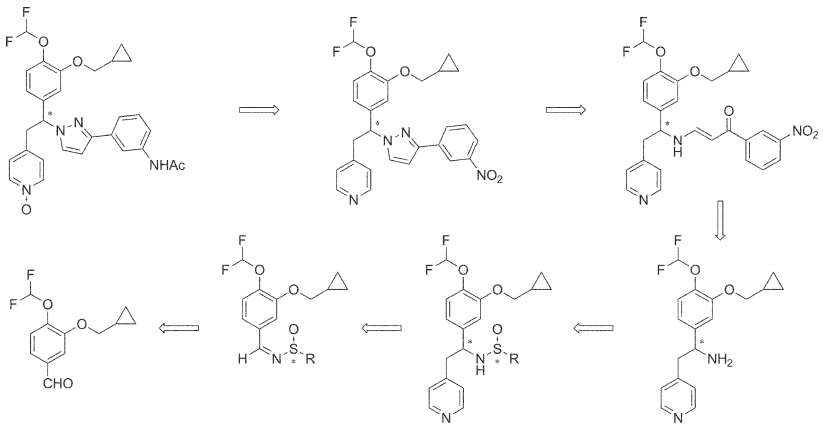
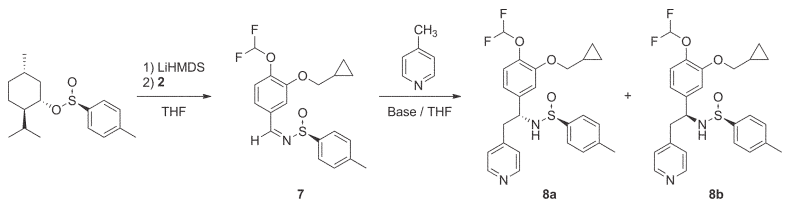


Fig. 3 Retrosynthesis of chiral pyrazoles **1*S*** and **1*R***.



Scheme 2 Synthesis of chiral *N*-*p*-toluenesulfinyl imine from chiral methyl *p*-toluenesulfinate and 4-picolyl lithium by an addition reaction to imine **7**.

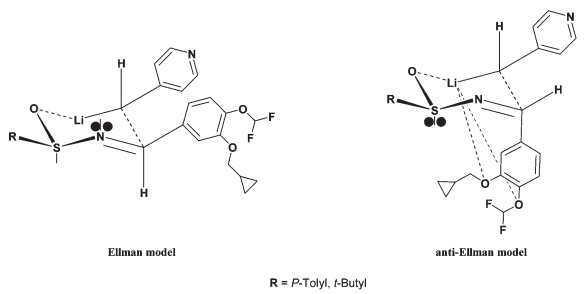
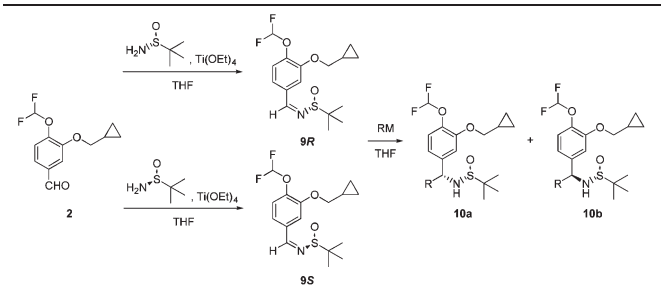


Fig. 4 Two proposed transition states for the reaction between sulfinimine and 4-picolyl lithium.

would play a major role, as proposed by Barrow *et al.* and shown in Fig. 4.[13]

Second, for the purpose of better diastereoselectivity and yield, we investigated *tert*-butanesulfinamide as a chiral auxiliary. (*R*)- and (*S*)-*N*-*tert*-butanesulfinamide were condensed with aldehyde **2** using titanium tetraethoxide as an additive in THF to generate (*R*)- and (*S*)-*N*-*tert*-butanesulfinimides **9*R*** and **9*S*** in good yields, as shown in Table 1. The synthesis of chiral amines through the addition of organometallic reagents to chiral *tert*-butanesulfinamide was studied by Ellman *et al.*[13a] This group demonstrated that chiral amines could be prepared in high yields with good diastereoselectivity from the reaction of a chiral *tert*-butanesulfinamide with diverse organometallic reagents. Taking into account the reported results, we investigated the addition reaction of methyllithium and methylmagnesium bromide to (*S*)-*N*-*tert*-butanesulfinimide **9*S*** in THF. Low diastereoselectivity (40% de) was observed with methyllithium in good yield, and

Table 1 The stereoselective addition of a metal carbanion to (*S*)-*N*-*tert*-butanesulfinimines[a]

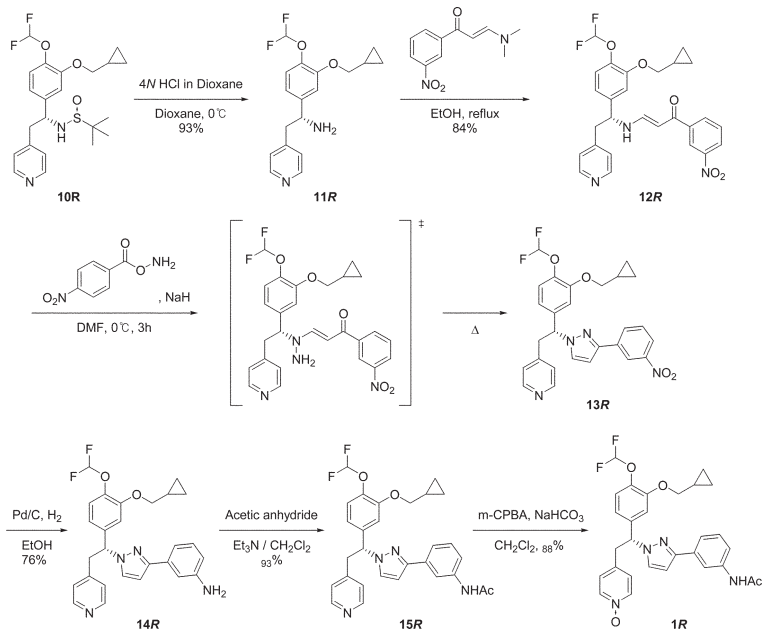


No.	Imine	RM	*N*-Sulfinamide **10a** : **10b**	Yield[b] (%)	% de[c]
1	**9*S***	MeMgBr	—	80	80
2	**9*S***	MeLi	—	92	40
3	**9*S***	PyMeLi	1 : 0	83	100
4	**9*R***	PyMeLi	0 : 1	82	100

[a] Typical reaction conditions: **9*R*** (7.5 mmol), PyMeLi (11.2 mmol), −78 °C, 3 h in THF. [b] Isolated yields. [c] Chiral HPLC analysis (CHIRALCEL OD, 0.46 × 25 cm (DAICEL)). A mobile phase of 10% IPA–*n*-hexane was passed through the column at 0.8 mL min^{-1}.

methylmagnesium bromide gave the optimized diastereoselectivity in 80% de, as listed in Table 1. We did not identify the relative isomeric structure of the diastereomer.

Surprisingly, the addition reaction of 4-picolyl lithium to **9*R*** and **9*S*** proceeded with high diastereoselectivity and led to pure **10a** or **10b** (100% de) in good yield. Two transition states for



Scheme 3 Synthetic method for **1*R*** from chiral sulfonamide.

the addition reaction of a carbanion to butanesulfinimines have been postulated, as shown in Fig. 4. The anti-Ellman models of the two transition states are known for a favored transition state in which the coordination of the lithium ion to the catechol portion of **9** would be a critical factor, as proposed by Barrow *et al.*[13] However, the reason for 4-picolyl lithium leading to extraordinarily high diastereoselectivity relative to that produced by methyllithium remains unclear. The sulfinyl group of **10*R*** was eliminated to give chiral amine **11*R*** by treatment with 4 N HCl solution in dioxane at 0 °C in 93% yield (Scheme 3). This reaction was followed by coupling with 3-dimethylamino-1-(3-nitrophenyl)propene to produce the *cis*-type enamine **12*R*** in 84% yield.[14] This type of enamine has been known to be stabilized by hydrogen bonding of the NH to the carbonyl group, and we confirmed that **12*R*** is the *cis*-type enamine by characteristic ^{1}H NMR (olefinic proton, δ 5.7, J = 7.5 Hz).

Diverse *N*-amination methods to yield amines have been previously reported.[15] However, *cis*-type enamine **12*R*** was inert to several amination reagents, such as *N*-Boc-oxaziridines, *O*-(mesitylenesulfonyl)hydroxylamine, and *tert*-butylnitrite. This enamine was only aminated by *O*-(*p*-nitrobenzoyl)hydroxyl amine and was followed with *in situ* thermal dehydrocyclization to produce pyrazole **13*R*** at 100 °C in DMF in 47% yield. Reduction of the nitro group in **13*R*** by a hydrogenation reaction using palladium catalyst proceeded and was followed by acylation of the amino group using acetic anhydride to generate **15*R*** in 93% yield. Compound **1*R*** was obtained by the oxidation of the pyridine moiety of **15*R*** using mCPBA in 88% yield. **1*S*** was prepared by the same synthetic method as that described for compound **1*R***.

In summary, we discovered a potent PDE4 inhibitor that includes a pyrazole moiety directly bonded to a chiral center. We studied the synthesis of racemic **1** and of chiral **1*S*** and **1*R*** using chiral *tert*-butanesulfinamide as a chiral auxiliary using a novel approach.

3. Experimental section

General methods

^{1}H NMR and ^{13}C NMR were recorded on Varian Gemini 200 (200 MHz ^{1}H) and 500 (500 MHz ^{1}H) spectrometers and a Bruker AM-300 spectrometer (^{13}C). Tetramethylsilane was used as an internal standard. IR spectra were recorded on a Travel IR Portable (ATR-FT IR Spectrometer System, Sens IR) spectrometer. Peaks are reported in units of cm^{-1}. Mass spectra (LMS) were recorded on a JEOL JMS-01 mass spectrometer, and HRMS were recorded on an Autospec Mass DX-300 mass spectrometer (Micromass) under electron-impact (EI) conditions. Optical rotations were recorded on Rudolph Autopol III (Automatic polarimeter) in the solvent indicated. Analytical HPLC was performed on a Jasco 880-PU Intelligent HPLC pump or a Jasco BIPP-1 HPLC pump equipped with a Jasco UVDEC-100-IV UV spectrometer or a Jasco UVDEC-100-UVV spectrometer. The columns used for this study included a Waters Optipak-XC, a Daicel OD-H, and a Daicel AD. Reactions were monitored by thin-layer chromatography performed on 0.25 mm Merck silica-gel plates (60F-254), which were imaged with UV light, ethanolic phosphomolybdic acid, or *p*-anisaldehyde and heat as the developing agent. Melting points were determined on a Buchi 510 melting-point apparatus and are uncorrected. Solvents were distilled before use. In anhydrous reactions, THF, ether, DME, and toluene were distilled from sodium metal benzophenone ketyl.

Synthesis of chiral *N*-(3-{1-[1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(1-oxypyridin-4-yl)ethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide (1)

(*R*)-4-Methylbenzenesulfinic acid 3-cyclopropylmethoxy-4-difluoromethoxybenzylideneamide (7). To a stirred solution of

(*1S*,*2R*,*5S*)-menthyl-(*R*)-*p*-toluenesulfinate (2.0 g, 8.2 mmol) in THF was added LiHMDS (11 mL, 11.5 mmol) dropwise at −78 °C and the reaction mixture was stirred for 2 h at 0 °C. **2** (2.0 g, 8.2 mmol) solution in THF was added dropwise to the reaction mixture at 0 °C and it was stirred for 12 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl, diluted with ethyl acetate (100 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (*n*-hexane–EA, 4 : 1) to give **7** (3.0 g, 95.8%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (1H, s, –CH), 7.63–7.59 (2H, m, Ar), 7.45 (1H, s, Ar), 7.34–7.08 (4H, m, Ar), 6.70 (1H, t, J = 72.5 Hz, $–CHF_2$), 3.87 (2H, d, J = 7.2 Hz, –OCH2–), 2.34 (3H, s, $–CH_3$), 1.25–1.23 (1H, m, –CH–), 0.63–0.59 (2H, m, $–CH_2–$), 0.34–0.32 (2H, m, $–CH_2–$); MS *m*/*z* (%) 379 (M^+, 1) 331 (1), 140 (20), 138 (100), 118 (2), 92 (4), 91 (8), 78 (1), 77 (4), 65 (2). 243 (6), 242 (11), 212 (2), 188 (5) 167 (5), 150 (6), 147 (7), 141 (60, 138 (100), 110 (1), 93 (42), 91 (8), 65 (3), 55 (23).

(*R*)-2-Methylpropane-2-sulfinic acid 3-cyclopropylmethoxy-4-difluoromethoxylbenzylideneamide (9*R*). To a stirred solution of **2** (2.0 g, 8.2 mmol) in THF was added $Ti(OEt)_4$ (37.0 g, 33.0 mmol), followed by dropwise (*R*)-2-methyl-2-propanesulfinamide (1.0 g, 8.2 mmol). The reaction mixture was stirred for 12 h at rt. The reaction solution was quenched with saturated aqueous NH_4Cl, diluted with ethyl acetate and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (*n*-hexane–EA, 5 : 1) to give **9*R*** (2.85 g, 99.8%).

$[\alpha]_D^{23}$ +204.6° (*c* 0.025, EtOH); IR (neat) ν_{max} 3085, 3013, 2983, 2901, 2873, 1737, 1598 1580, 1509, 1430, 1270, 1111, 1077, 1047, 1024, 1008, 906.3 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (1H, s, –NCH), 7.47 (1H, d, J = 1.8 Hz, Ar), 7.41–7.39 (1H, m, Ar), 7.27–7.25 (1H, m, Ar), 6.72 (1H, t, J = 74.9 Hz, $–CHF_2$), 3.95 (2H, d, J = 6.9 Hz, $–OCH_2–$), 1.32–1.27 (1H, m, –CH–), 1.26 (9H, s, 3 $–CH_3$), 0.69–0.66 (2H, m, $–CH_2–$), 0.41–0.38 (2H, m, $–CH_2–$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 161.6, 150.8, 132.3, 123.4, 122.5, 117.8, 115.8, 113.7, 74.0, 57.9, 22.6, 10.0, 3.2; MS *m*/*z* (%) 289 (M^+, 98), 288 (5), 272 (4), 241 (20), 240 (22), 212 (7), 187 (11), 184 (5), 167 (8), 149 (3), 97 (2), 84 (7), 71 (4), 55 (90); HRMS calcd for $C_{16}H_{21}F_2NO_3S$: 345.1210, found: 345.1213.

(*S*)-2-Methylpropane-2-sulfinic acid 3-cyclopropylmethoxy-4-difluoromethoxylbenzylideneamide (9*S*). Prepared as described for compound **9*R*** (8.2 mmol scale, 98.8% yield).

$[\alpha]_D^{23}$ −206.0° (*c* 0.025, EtOH); All spectra were identical to those of compound **9*R***.

(*R*,*R*)-2-Methylpropane-2-sulfinic acid [1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-yl-ethyl]amide (10*R*). To a stirred solution of 4-methylpyridine (1.1 g, 11.2 mmol) in THF was added *n*-BuLi (6.1 mL, 9.8 mmol) dropwise at −78 °C and the reaction mixture was stirred for 0.5 h at 0 °C. After cooling to −78 °C, **9*R*** (2.6 g, 7.5 mmol) solution in THF was added dropwise to the reaction mixture and stirred for 3 h at −78 °C. The reaction solution was quenched with saturated aqueous NH_4Cl, diluted with ethyl acetate (100 mL) and washed with water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (*n*-hexane–EA, 2 : 1) to give **10*R*** (2.78 g, 82%).

$[\alpha]_D^{23}$ −30.0° (*c* 0.025, EtOH); IR (neat) ν_{max} 3206, 2955, 2927, 2871, 1735, 1602, 1562, 1509, 1467, 1413, 1386, 1215, 1116, 1045, 915, 835, 730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42–8.41 (2H, m, Ar), 7.08 (1H, d, J = 8.2 Hz, Ar), 6.97–6.96 (2H, m, Ar), 6.85–6.83 (1H, m, Ar), 6.80 (1H, d, J = 1.9 Hz, Ar), 6.60 (1H, t, J = 75.4 Hz, $–CHF_2$), 4.58 (1H, d, J = 4.6 Hz, –CH–), 3.76 (2H, d, J = 6.9 Hz, $–OCH_2–$), 3.73 (1H, d, J = 4.6 Hz, –NH–), 3.29–3.25 (1H, m, dd, $–CH_2–$), 3.01–2.97 (1H, m, dd, $–CH_2$), 1.18–1.15 (1H, m, –CH–), 1.15 (9H, s, $–CH_3$, $–CH_3$, $–CH_3$), 0.61–0.59 (1H, m, $–CH_2–$), 0.32–0.31 (1H, m, $–CH_2–$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.4, 149.6, 146.4, 140.1, 139.7, 124.9, 122.7, 119.3, 118.2, 116.1, 114.1, 113.8, 73.8, 59.8, 56.1, 42.7, 22.5, 10.0, 3.1; MS *m*/*z* (%) 438 (M+, 40), 391 (11), 383 (92), 346 (37), 320 (80), 291 (77), 288 (75), 265 (100), 242 (80), 213 (72), 188 (97), 166 (77), 147 (83), 141 (25), 106 (68), 92 (42), 56 (49); HRMS calcd for $C_{22}H_{28}F_2N_2O_3S$: 438.1789, found: 438.1782.

(*S*,*S*)-2-Methylpropane-2-sulfinic acid [1-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-yl-ethyl]amide (10*S*). Prepared as described for compound **10*R*** (8.2 mmol scale, 83% yield).

$[\alpha]_D^{23}$ +30.6° (*c* 0.025, EtOH); IR (neat) ν_{max} 3207, 3078, 2956, 2872, 2358, 2228, 1602, 1563, 1509, 1467, 1413, 1386, 1270, 1215, 1116 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.67 (1H, s, –CH), 7.63–7.59 (2H, m, Ar), 7.45 (1H, s, Ar) 7.34–7.08 (3H, m, Ar), 6.70 (1H, t, J = 72.4 Hz, $–CHF_2$), 3.87 (2H, d, J = 7.2 Hz, $–OCH_2–$), 2.35 (3H, s, $–CH_3$) 1.25–1.23 (1H, m, –CH–), 0.63–0.59 (1H, m, $–CH_2–$), 0.34–0.32 (1H, m, $–CH_2–$); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.5, 149.7, 146,4, 140.1, 139.7, 124.9, 122.8, 119.3, 118.2, 116.2, 114.1, 113.9, 73.9, 59.8, 56.2, 42.7, 22.5, 10.1, 3.2; MS *m*/*z* (%) 438 (M^+, 8), 391 (3), 382 (58), 346 (5), 319 (80), 289 (80), 240 (35), 235 (15), 187 (17), 167 (35), 149 (30), 94 (70), 55 (100); HRMS calcd for $C_{22}H_{28}F_2N_2O_3S$: 438.1789, found: 438.1783.

(*R*)-1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethylamine (11*R*). 4*N*-HCl (4.1 mL, 16.4 mmol) was added slowly to a solution of **10*R*** (1.8 g, 4.1 mmol) in dioxane at 0 °C. After 5 min, the cooling bath was removed. The reaction was allowed to ambient temperature and stirred for 4 h. The solid formed during the reaction was filtered up and added to saturated aqueous $NaHCO_3$, extracted with ethyl acetate. The organic phase was washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 20 : 1) to give **11*R*** (1.2 g, 93.6%).

$[\alpha]_D^{23}$ −316.8° (*c* 0.03, EtOH); IR (neat) ν_{max} 3073, 3016, 2926, 2874, 1734, 1666, 1600, 1562, 1506, 1469, 1422, 1411, 1380, 1269, 1207, 1112, 1016 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (2H, d, J = 5.8 Hz, Ar), 7.10 (1H, d, J = 8.2 Hz, Ar), 7.06–7.05 (2H, m, Ar), 6.91 (1H, d, J = 1.9 Hz, Ar), 6.86–6.84 (1H, m, Ar), 6.61 (1H, t, J = 75.6 Hz, $–CHF_2$),

4.21–4.18 (1H, m, –CH–), 3.84 (2H, d, J = 3.6 Hz, –OCH_2–), 2.93–2.90 (1H, m, dd, –CH_2–), 2.84–2.81 (1H, m, dd, –CH_2), 1.68 (2H, s, –NH_2), 1.24–1.20 (1H, m, –CH–), 0.64–0.61 (1H, m, –CH_2–), 0.35–0.33(1H, m, –CH_2–); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.5, 149.7, 147,6, 143.4, 139.5, 124.6, 122.6, 118.9, 116.2, 112.4, 73.9, 56.5, 45.7, 10.1, 3.1; MS m/z (%) 334 (M^+, 12), 306 (7), 296 (60), 268 (60), 243 (100), 242 (45), 214 (22), 188 (80), 168 (25), 147 (87), 121 (48), 107 (40), 88 (70) 57 (55); HRMS calcd for $C_{18}H_{20}F_2N_2O_2$: 334.1493, found: 334.1486.

(*S*)-1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethylamine (11*S*). Prepared as described for compound **11*R*** (3.1 mmol scale, 82% yield).

$[\alpha]_D^{23}$ +314.8° (c 0.03, EtOH); All spectra were identical to those of compound **11*R***.

(*R*)-3-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethylamino]-1-(3-nitrophenyl)propenone (12*R*). Compound **11*R*** (1.0 g, 2.8 mmol) and (*E*)-3-(*N*,*N*-dimethylamino-1-(4-nitrophenyl)-2-propen-1-one (0.6 g, 2.8 mmol) were refluxed in ethanol for 12 h. The reaction was allowed to cool to the ambient temperature and was quenched by adding water then concentrated *in vacuo*. The mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 80 : 1) to afford 12*R* (1.2 g, 84.2%).

$[\alpha]_D^{23}$ −120.8° (c 0.025, EtOH); IR (neat) ν_{max} 3232, 3078, 3018, 2928, 1733, 1626, 1585, 1525, 1500, 1427, 1380, 1347, 1267, 1109, 1044, 1021, 1005, 911, 810, 782, 724 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.67 (1H, d, J = 1.8 Hz, Ar), 8.53–8.52 (2H, m, Ar), 8.31–8.28 (1H, m, Ar), 8.18–8.16 (1H, m, Ar), 7.62–7.58 (1H, m, Ar), 7.17 (1H, d, J = 8.2 Hz, olefinic-H), 7.09–7.08 (1H, m, Ar), 6.86–6.79 (3H, m, Ar) 6.62 (1H, t, J = 75.3 Hz, –CHF_2), 5.70 (1H, d, J = 7.5 Hz, olefinic-H), 4.54–4.49 (1H, m, –CH–), 3.84 (2H, d, J = 6.9 Hz, –OCH_2–), 3.16 (1H, d, J = 7.2 Hz, –CH_2), 1.65 (1H, s, –NH–), 1.27–1.21 (1H, m, –CH–), 0.66–0.62 (1H, m, –CH_2–), 0.36–0.33 (1H, m, –CH_2–); ^{13}C NMR (500 MHz, $CDCl_3$) δ 187.3, 153.7, 151.0, 150.1, 148.3, 145,5, 140.8, 138.9, 132.8, 129.4, 125.5, 124.6, 123.2, 122.1, 119.1, 116.0, 113.9, 112.6, 91.1, 74.1, 63.7, 43.5, 10.0, 3.2; MS m/z (%) 509 (M^+, 10), 479 (4), 417 (100), 387 (38), 363 (25), 333 (40), 318 (12), 296 (4), 264 (5), 242 (6), 212 (3), 196 (7), 167 (8), 150 (22), 147 (13), 93 (48), 92 (5), 55 (75); HRMS calcd for $C_{27}H_{25}F_2N_3O_5$: 509.1762, found: 509.1763.

(*S*)-3-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethylamino]-1-(3-nitrophenyl)propenone (12*S*). Prepared as described for compound **12*R*** (2.2 mmol scale, 89% yield).

$[\alpha]_D^{23}$ +121.8° (c 0.025, EtOH); All spectra were identical to those of compound **12*R***.

(*R*)-4-{2-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-[3-(3-nitrophenyl)-pyrazol-1-yl]-ethyl}pyridine (13*R*). To a stirred solution of **12*R*** (1.1 g, 2.1 mmol) in DMF was added NaH (0.2 g, 4.2 mmol) slowly at 0 °C and the reaction mixture was stirred for 1 h at 0 °C. *O*-(4-Nitrobenzoyl)hydroxylamine (0.9 g, 4.2 mmol) was added slowly to the reaction mixture and stirred for 3 h at 0 °C, followed by heating for 10 min. The reaction was allowed to cool to ambient temperature and was quenched with saturated aqueous NH_4Cl, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (*n*-hexane–EA, 1 : 2) to give **13*R*** (0.5 g, 47.4%).

$[\alpha]_D^{23}$ −191.0° (c 0.015, EtOH); IR (neat) ν_{max} 3078, 3017, 2927, 1732, 1602, 1531, 1512, 1432, 1411, 1379, 1346, 1215, 1115, 1047, 1019, 907, 862, 808, 763, 732, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70–8.69 (1H, m, Ar), 8.45 (2H, d, J = 5.7 Hz, Ar), 8.17–8.15 (1H, m, Ar), 8.13 (1H, d, J = 7.8 Hz, Ar), 7.59–7.56 (1H, m, Ar), 7.34 (1H, d, J = 2.3 Hz, Ar), 7.13 (1H, d, J = 8.2 Hz, Ar), 7.08 (1H, d, J = 1.9 Hz, Ar), 6.99 (2H, d, J = 5.6 Hz, Ar), 6.94–6.92 (1H, m, Ar), 6.61 (1H, t, J = 75.3 Hz, –CHF_2), 6.58 (1H, d, J = 2.3 Hz, Ar), 5.41–5.38 (1H, m, –CH–), 3.93–3.90 (1H, m, dd, –CH_2–), 3.86 (2H, d, J = 4.6 Hz, –OCH_2–), 3.42–3.39 (1H, m, dd, –CH_2), 1.26–1.23 (1H, m, –CH–), 0.62–0.60 (1H, m, –CH_2–), 0.34–0.33 (1H, m, –CH_2–); ^{13}C NMR (500 MHz, $CDCl_3$) δ 150.8, 150.0, 149.6, 148.9, 146,6, 140.5, 138.0, 135.4, 131.4, 129.7, 124.4, 122.9, 122.4, 120.5, 119.6, 118.2, 116.2, 113.5, 103.6, 74.1, 67.0, 41.5, 10.2, 3.4; MS m/z (%) 506 (M^+, 75) 476 (25), 452 (24), 451 (6), 414 (99), 384 (30), 360 (35), 359 (6), 317 (65), 297 (25), 263 (24), 251 (42), 243 (10), 212 (6), 197 (13), 167 (15), 149(9), 147 (5), 97 (7), 71 (11), 55 (100); HRMS calcd for $C_{27}H_{24}F_2N_4O_4$: 506.1766, found: 509.1753.

(*S*)-4-{2-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-[3-(3-nitrophenyl)-pyrazol-1-yl]-ethyl}-pyridine (13*S*). Prepared as described for compound **13*R*** (1.7 mmol scale, 47% yield).

$[\alpha]_D^{23}$ +195.0° (c 0.015, EtOH); All spectra were identical to those of compound **13*R***.

(*R*)-3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethyl]-1*H*-pyrazol-3-yl}phenylamine (14*R*). To a stirred solution of **13*R*** (0.4 g, 0.79 mmol) in EtOH was added 10% Pd/C followed by being charged with hydrogen gas. The resulting mixture was stirred at ambient temperature for 5 h and filtered. The filtrate was diluted with ethyl acetate and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 20 : 1) to give **14*R*** (0.29 g, 76%).

$[\alpha]_D^{23}$ −89.0° (c 0.015, EtOH);); IR (neat) ν_{max} 3215, 3026, 2927, 1729, 1604, 1561, 1510, 1477, 1449, 1432, 13829, 1347, 1267, 1206, 1112, 1047, 1025, 907, 807, 786, 757, 727, 691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (2H, d, J = 5.9 Hz, Ar), 7.32–7.31 (1H, m, Ar), 7.26–7.25 (3H, m, Ar), 7.17 (1H, d, J = 8.2 Hz, Ar), 7.08 (1H, d, J = 2.0 Hz, Ar), 7.03 (1H, d, J = 5.9 Hz, Ar), 6.98 (2H, d, J = 2.0 Hz, Ar), 6.96 (1H, d, J = 2.0 Hz, Ar), 6.73–6.72 (1H, m, Ar), 6.65 (1H, t, J = 75.4 Hz, –CHF_2), 6.73–6.71 (1H, m, Ar), 5.44–5.41 (1H, m, –CH–), 4.00–3.95 (1H, m, dd, –CH_2–), 3.87 (2H, d, J = 6.9 Hz, –OCH_2–), 3.42–3.38 (1H, m, dd, –CH_2), 1.32–1.26 (1H, m, –CH–), 0.67–0.65 (1H, m, –CH_2–), 0.39–0.37 (1H, m, –CH_2–); ^{13}C NMR (500 MHz, $CDCl_3$) δ 152.0, 150.8, 149.9, 146,8,

140.3, 138.6, 134.7, 130.7, 129.7, 124.5, 122.8, 119.5, 118.3, 116.3, 116.2, 114.8, 113.5, 112.3 103.2, 74.0, 66.6, 41.5, 10.2, 3.3; MS *m*/*z* (%) 476 (M^+, 90), 421 (7), 414 (3), 384 (99), 356 (3), 318 (30), 317 (12), 297 (5), 263 (23), 243 (8), 207 (15), 197 (13), 170 (15), 149 (16), 147 (15), 135 (12), 84 (100), 55 (60); HRMS calcd for $C_{27}H_{26}F_2N_4O_2$: 476.2024, found: 476.2021.

(*S*)-3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-ylethyl]-1*H*-pyrazol-3-yl}phenylamine (14*S*). Prepared as described for compound **14*R*** (0.6 mmol scale, 77% yield).

$[\alpha]_D^{23}$ +86.3° (*c* 0.015, EtOH); All spectra were identical to those of compound **14*R***.

(*R*)-*N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-yl-ethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide (15*R*). To a stirred solution of **14*R*** (0.15 g, 0.31 mmol) in CH_2Cl_2 was added acetic anhydride (0.038 g, 0.38 mmol) and Et_3N (0.047 g, 0.47 mmol). Afterwards the reaction was stirred for 12 h at rt, quenched with saturated aqueous $NaHCO_3$, diluted with ethyl acetate and washed water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 40 : 1) to give **15*R*** (0.15 g, 93.3%).

$[\alpha]_D^{23}$ −149.7° (*c* 0.018, EtOH); IR (neat) ν_{max} 3091, 2365, 2329, 2129, 1986, 1794, 1606, 1554, 1507, 1466, 1415, 1375, 1271, 1119, 1111, 1043, 999, 855, 796, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (2H, d, J = 5.5 Hz, Ar), 7.99 (1H, s, Ar), 7.55–7.50 (2H, m, Ar), 7.34–7.31 (1H, m, Ar), 7.26–7.25 (1H, m, Ar), 7.09 (1H, d, J = 8.2 Hz, Ar), 7.01 (1H, d, J = 1.9 Hz, Ar), 6.96 (2H, d, J = 5.7 Hz, Ar), 6.90–6.88 (1H, m, Ar), 6.59 (1H, t, J = 75.4 Hz, –CHF_2), 6.46 (1H, d, J = 2.2 Hz, Ar), 5.37–5.34 (1H, m, –CH–), 3.90–3.86 (1H, m, dd, –CH_2–), 3.80 (2H, d, J = 6.9 Hz, –OCH_2–), 3.50–3.24 (1H, m, dd, –CH_2), 2.16 (3H, s, –CH_3) 1.25–1.17 (1H, m, –CH–), 0.60–0.56 (1H, m, –CH_2–), 0.31–0.28 (1H, m, –CH_2–); ^{13}C NMR (500 MHz, $CDCl_3$) δ 168.7, 151.4, 150.7, 149.9, 146.9, 140.3, 138.6, 138.5, 134.4, 130.9, 129.4, 124.5, 122.8, 121.6, 119.5, 117.1, 116.2, 114.2, 113.5, 103.2, 74.0, 66.6, 41.5, 24.7, 10.2, 3.3; MS *m*/*z* (%) 518 (M^+, 64), 464 (7), 463 (7), 426 (100), 398 (6), 372 (12), 334 (6), 317 (40), 297 (13), 263 (22), 251 (18), 243 (10), 197 (16), 159 (26), 154 (5), 130 (10), 93 (5), 77 (4), 55 (80); HRMS calcd for $C_{29}H_{28}F_2N_4O_3$: 518.2129, found: 518.2115.

(*S*)-*N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-pyridin-4-yl-ethyl]-1*H*-pyrazol-3-yl}phenyl)acetamide (15*S*). Prepared as described for compound **15*R*** (0.25 mmol scale, 96% yield).

$[\alpha]_D^{23}$ +148.8° (*c* 0.018, EtOH); All spectra were identical to those of compound **15*R***.

(*R*)-*N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(1-oxypyridin-4-yl)-ethyl]-1*H*-pyrazol-3-yl-phenyl)acetamide (1*R*). To a stirred solution of **15*R*** (0.10 g, 0.19 mmol) in CH_2Cl_2 was added MCPBA (0.071 g, 0.028 mmol) and $NaHCO_3$ (0.024 g, 0.028 mmol). After stirring for 12 h at rt, the reaction was quenched with saturated aqueous $NaHCO_3$, diluted with ethyl acetate and washed with water and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 20 : 1) to give **1*R*** (0.089 g, 88.7%).

$[\alpha]_D^{23}$ −122.0° (*c* 0.018, EtOH); IR (neat) ν_{max} 3010, 2167, 2036, 1541, 1276, 1261, 764, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03–8.01 (2H, m, Ar), 7.93 (1H, s, Ar), 7.52–7.48 (2H, m, Ar), 7.34–7.31 (1H, m, Ar), 7.24 (1H, d, J = 2.2 Hz, Ar), 7.13 (1H, d, J = 8.2 Hz, Ar), 7.05 (1H, d, J = 1.9 Hz, Ar), 6.96–6.91 (3H, m, Ar), 6.61 (1H, t, J = 75.3 Hz, –CHF_2), 6.47 (1H, d, J = 2.3 Hz, Ar), 5.33–5.29 (1H, m, –CH–), 3.87–3.86 (1H, m, dd, –CH_2–), 3.84 (2H, d, J = 6.9 Hz, –OCH_2–), 3.33–3.29 (1H, m, dd, –CH_2), 2.18 (3H, s, –CH_3) 1.25–1.20 (1H, m, –CH–), 0.62–0.58 (1H, m, –CH_2–), 0.33–0.30 (1H, m, –CH_2–); ^{13}C NMR (500 MHz, $CDCl_3$) δ 168.9, 151.6, 150.9, 140.4, 139.0, 138.9, 138.0, 134.2, 131.0, 129.4, 127.0, 122.9, 121.4, 119.5, 119.4, 117.1, 116.1, 114.2, 113.4, 103.6, 74.1, 66.4, 40.6, 24.6, 10.2, 3.3; MS *m*/*z* (%) 534 (M^+, 52), 518 (72), 464 (5), 426 (100), 372 (12), 317 (32), 297 (10), 263 (30), 251 (18), 243 (7), 197 (12), 184 (8), 159 (25), 130 (8), 104 (3), 93 (10), 92 (7), 55 (78); HRMS calcd for $C_{29}H_{28}F_2N_4O_4$: 534.2079 found: 534.2065.

(*S*)-*N*-(3-{1-[1-(3-Cyclopropylmethoxy-4-difluoromethoxyphenyl)-2-(1-oxypyridin-4-yl)-ethyl]-1*H*-pyrazl-3-yl-phenyl)acetamide (1*S*). Prepared as described for compound **1*R*** (0.15 mmol scale, 85% yield).

$[\alpha]_D^{23}$ +120.85° (*c* 0.018, EtOH); All spectra were identical to those of compound **1*R***.

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