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Graphical Abstract

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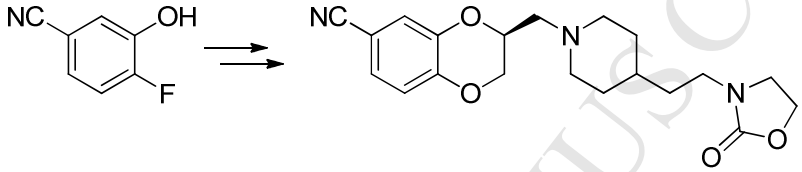
Julien Alliot[a], Edmond Gravel[a], David-Alexandre Buisson[a], Laurent Larquetoux[b], Marc Nicolas[b], and Eric Doris[a,*]

[a] *CEA, iBiTecS, Service de Chimie Bioorganique et de Marquage, 91191 Gif-sur-Yvette, France. eric.doris@cea.fr*

[b] *Les Laboratoires Pierre Fabre, Centre de Développement de Chimie Industrielle, 16 rue Jean Rostand, 81600 Gaillac, France*



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[b] *Les Laboratoires Pierre Fabre, Centre de Développement de Chimie Industrielle, 16 rue Jean Rostand, 81600 Gaillac, France*

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ABSTRACT

An efficient approach for the enantioselective synthesis of the 1,4-benzodioxane F17807 drug is reported. The developed route relied on two key steps, namely S_NAr and Mitsunobu reactions, which permitted a straightforward access to the title compound with full preservation of the enantiomeric excess throughout the synthetic sequence.

1. Introduction

The 1,4-benzodioxane motif is routinely found not only in naturally occurring compounds such as silybin A (**1**) which is extracted from *Silybum marianum*,[1] but also in synthetic drugs as WB4101 (**2**)[2] and doxazosin (**3**)[3] (treatment of hypertension), or fluparoxan (**4**)[4] (antidepressant) (Figure 1). Also, Pierre Fabre laboratories have recently developed a series of 1,4-benzodioxane derivatives that are currently evaluated for the treatment of neuropsychiatric disorders such as schizophrenia.[5] One of the lead compounds among the series is F17807 (**5**).

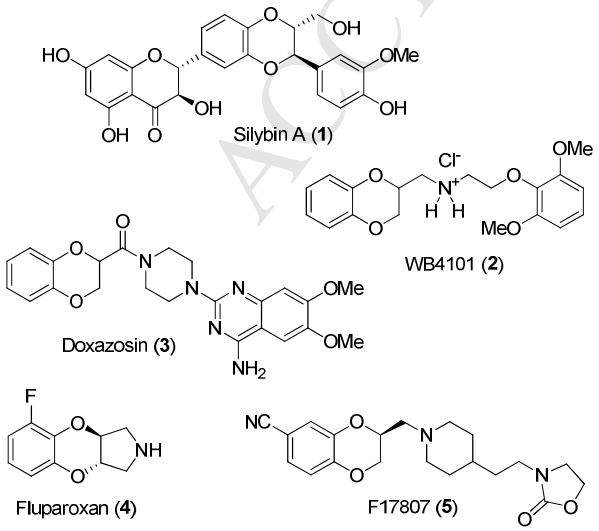


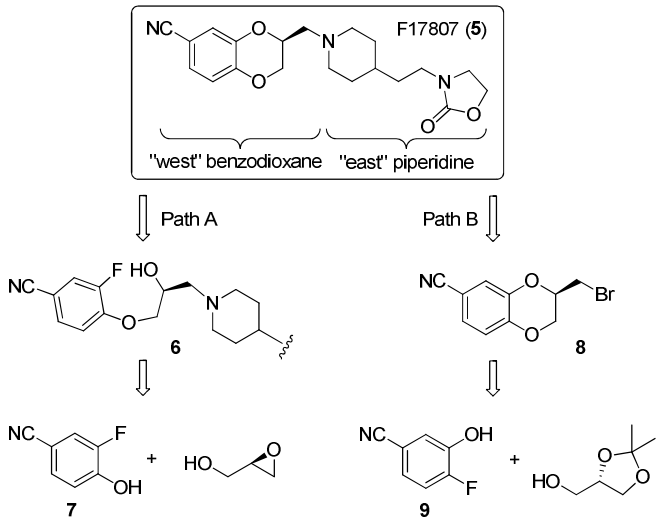
Figure 1. Example of 1,4-benzodioxane derivatives.

The first synthesis (in its racemic form) of a 1,4-benzodioxane derivative was reported by Moureu in 1899 when studying the thermal degradation of 2-(2,2-diethoxypropoxy)phenol.[6] More generally, substituted racemic benzodioxanes can be prepared by condensation of catechol derivatives with various electrophiles,[7–11] or by organometallic tandem ring opening/coupling of epoxides using α-halogenophenols.[12,13] In addition, access to optically active 1,4-benzodioxanes can be achieved by chemical[14] and enzymatic kinetic resolution[15] of the racemate or by condensing optically active glycidyl tosylate[16] with catechols. Other approaches involve, for example, chiral palladium-complexes to catalyze C-O bond formation,[17] and Sharpless asymmetric epoxidation.[18] Although efficient, the above routes are not fully satisfactory as kinetic resolution leads to the loss of at least half of the material, and erosion of enantiomeric purity is sometimes observed in the other cases. With these features in mind and as part of our ongoing interest in the synthesis of bioactive compounds,[19] we sought to investigate an efficient and original route for the enantioselective synthesis of F17807 (**5**).

2. Results and discussion

The structure of F17807 is composed of two blocks, *i.e.* a "west" 1,4-benzodioxane fragment bearing the chiral centre, and an "east" piperidine fragment. Our strategy for the construction of the key 1,4-benzodioxane core in its optically active form relies on both the use of intramolecular S_NAr and Mitsunobu reactions. Two approaches were investigated, one starting from glycidol as chiral source (Scheme 1, Path A) and the other from isopropylidene glycerol (Scheme 1, Path B). In Path A, the

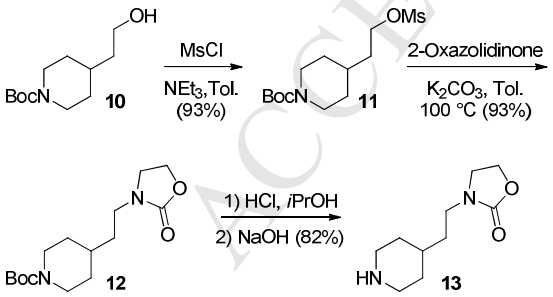
benzodioxane ring is planned to be constructed in the final stage of the synthesis by an intramolecular S_NAr reaction on **6**. The latter intermediate could originate from Mitsunobu coupling of (*R*)-glycidol with phenol derivative **7**, followed by ring opening of the epoxide with the piperidine unit.



Scheme 1. Possible synthetic pathways to F17807.

In path B on the other hand, the piperidine unit is connected to an already formed benzodioxane ring **8** that could originate from sequential S_NAr coupling between **9** and (*S*)-isopropylidene glycerol, removal of the isopropylidene protecting group, selective activation of the primary alcohol, and Mitsunobu coupling.

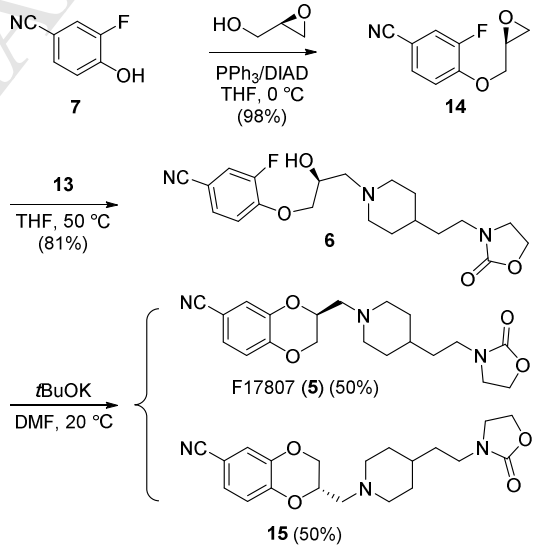
We first explored the route described in Path A (Scheme 1). Our synthesis commenced with the three-step synthesis of the piperidine "eastern" fragment from commercially available *N*-Boc-4-piperidine ethanol **10** (Scheme 2). The primary alcohol was activated as the corresponding mesylate **11** before nucleophilic substitution by 2-oxazolidinone under alkaline conditions. The Boc-protecting group was finally removed using HCl in *i*PrOH to afford, after neutralization with NaOH, the expected piperidine **13** in 71% overall yield.



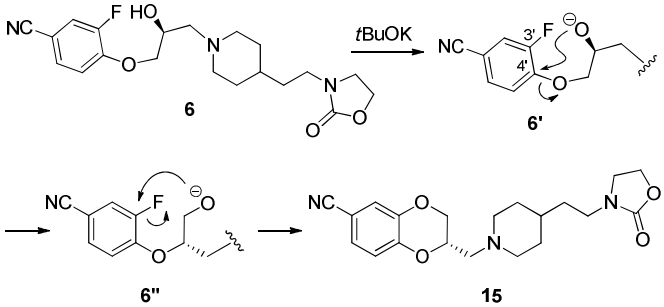
Scheme 2. Synthesis of the piperidine "east" fragment **13**.

In parallel to the synthesis of the piperidine fragment, the condensation of 3-fluoro-4-hydroxybenzonitrile **7** with (*R*)-glycidol under Mitsunobu conditions (PPh_3/DIAD) led to epoxy-ether **14** in which the stereogenic centre is set (Scheme 3). The epoxide unit was subsequently ring-opened with the above prepared piperidine fragment **13**. The substitution reaction proceeded regioselectively at the less hindered position of the epoxide to afford **6** as a single regioisomer. With compound **6** in hands, we next looked at the key S_NAr reaction for the benzodioxane ring-closing step. Compound **6** was thus reacted with *t*BuOK in DMF at room temperature, but surprisingly a 1:1 mixture of isomers was obtained and the products could not be separated by chromatography (Scheme 3). Changing the solvent (*e.g.* DMSO, THF, CH_3CN), base (*e.g.* DBU, NaH, KHMDS), and temperature (room temperature to reflux) conditions did not improve the selectivity of the reaction. Although the expected compound F17807 (**5**) was produced in the course of the transformation, *ca.* 50% of the cyclized benzodioxane product corresponded to a rearranged derivative to which we tentatively assigned the structure of compound **15**.

The formation of the latter compound can be rationalized by initial deprotonation of the secondary alcohol of **6** to afford alcoholate **6'** (Scheme 4). While the S_NAr reaction of the alcoholate on the fluorine-bearing C3' leads to the formation F17807, its addition to the more activated C4'-position (*para* to the CN group) induces the formation of a rearranged compound **6''** with the concomitant release of a primary alcoholate. The ensuing addition of the newly released alcoholate on C3', followed by fluorine elimination finally leads to the formation of isomer **15**. Although absolute configurations of the two products (namely **5** and **15**) could not be unambiguously established after the key cyclization step (products could not be separated by chromatography), the proposed mechanism suggests that the stereogenic center borne by compound **6** remains unaffected throughout the S_NAr process.

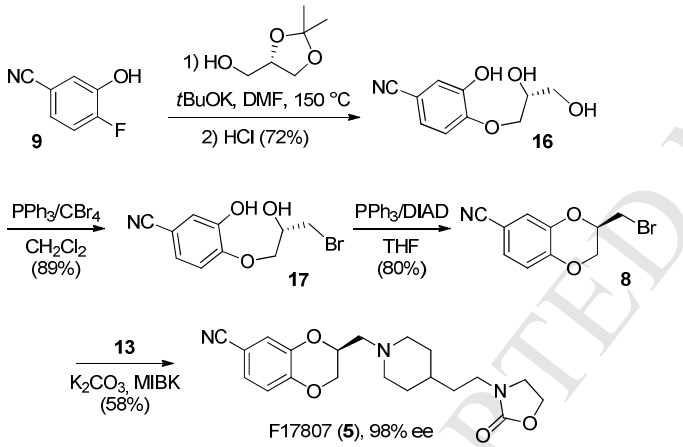


Scheme 3. Realization of path A synthesis.



Scheme 4. Proposed mechanism for the formation of rearranged compound **15**.

As our initial scheme did not work out as anticipated because of the preferential nucleophilic addition of the alcoholate to the C4'-position, we conceived that the S_NAr reaction could be more efficiently promoted starting from 4-fluoro-3-hydroxybenzonitrile **9** in which the leaving fluorine atom is properly positioned *para* to the cyano group. Thus, 4-fluoro-3-hydroxybenzonitrile **9** was first reacted under basic conditions (*t*BuOK) with the more robust glycidol-equivalent (*S*)-isopropylidene glycerol (98% ee) (Scheme 5). Although the reaction proceeded at 150 °C, it cleanly gave access to the key intermediate **16**, after deprotection of the 1,2-diol. It is to be noted that, contrary to previous reports,[20] the above S_NAr reaction did not require protection of the phenol group, thus allowing a more direct route to the target compound. The primary alcohol of **16** was then selectively brominated by PPh_3/CBr_4 (compound **17**). This step permitted to differentiate secondary from primary alcohols prior to the intramolecular coupling with the phenol unit. The remaining optically active secondary alcohol was then activated under Mitsunobu's conditions and underwent smooth coupling with the neighboring phenol to give access to optically active 1,4-benzodioxane **8** where the stereogenic centre is irreversibly set. Of note, the S_N2 reaction proceeded with inversion of configuration of the alcohol-bearing centre. The synthesis of F17807 (**5**) was finally completed by the coupling of **8** with piperidine **13** at 110 °C in methyl isobutyl ketone. F17807 (**5**) was obtained in seven steps, with a satisfactory overall yield of 21% but more importantly with a retained enantiomeric excess of 98%.



Scheme 5. Realization of path B synthesis.

3. Conclusions

We reported here an efficient enantioselective synthesis of F17807 from 4-fluoro-3-hydroxybenzonitrile and (*S*)-isopropylidene glycerol. Our approach is based on two key coupling steps, namely S_NAr and Mitsunobu reactions. The enantiomeric excess of the starting isopropylidene glycerol was preserved throughout the synthetic pathway, thus permitting efficient access to 1,4-benzodioxane F17807 with 98% ee.

4. Experimental

4.1. General

Reactions were carried out under nitrogen using dry solvents, unless otherwise stated. THF was distilled from sodium/benzophenone before use. Flash chromatography was carried out on Kieselgel 60 (230–240 mesh, Merck) and analytical TLC was performed on Merck precoated silica gel (60 F254). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts (δ) are given in ppm and coupling constants (J) in hertz. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR System. Optical rotations were determined using the sodium D line (589 nm) on a Perkin Elmer 341 polarimeter.

4.2. N-*Boc-4-(2-((methylsulfonyl)oxy)ethyl)piperidine (**11**).*

At room temp. under N_2, mesyl chloride (0.52 mL, 2 equiv.) was added dropwise to a solution of *N*-Boc piperidine ethanol **10** (840 mg, 3.7 mmol, 1.0 equiv.) and triethylamine (1.0 mL, 2 equiv.) in 20 mL anhydrous toluene. The solution was stirred for 4 h and was quenched with 20 mL 1 M HCl. The aqueous phase was extracted with EtOAc (3 × 20 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residual oil was crystallized from heptane (40 mL) to afford **11** (1.05 g, 93%). ^{1}H-NMR ($CDCl_3$): δ 4.30 (t, J = 6.4 Hz, 2H), 3.04 (s, 3H), 2.71 (t, J = 12.5 Hz, 2H), 1.75−1.60 (m, 7H), 1.47 (s, 9H), 1.21−1.15 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 154.8, 79.4, 77.4, 67.4, 37.5, 35.6, 32.4, 31.7, 28.5. IR (neat): 2925, 1775, 1682 cm^{-1}. ESI-MS (ES$^+$): 308 [M+H]$^+$.

4.3. N-*Boc-4-(2-(2-oxooxazolidin-3-yl)ethyl)piperidine (**12**).*

Under N_2, 2-oxazolidinone (321 mg, 1.2 equiv.) and K_2CO_3 (511 mg, 1.2 equiv.) were added to a solution of **11** (950 mg, 3.1 mmol, 1.0 equiv.) in 10 mL anhydrous toluene. The suspension was heated at 100 °C for 17 h. H_2O (20 mL) was then added and the the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by flash chromatography (Et_2O/MeOH, 100:0 to 95:5) to afford **12** (860 mg, 93%). ^{1}H-NMR ($CDCl_3$): δ 4.35 (t, J = 7.9 Hz, 2H), 3.56 (t, J = 8.1 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H), 2.71 (t, J = 11.7 Hz, 2H), 1.75−1.68 (m, 2H), 1.54−1.41 (m, 14H), 1.22−1.09 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 158.4, 154.8, 79.3, 77.3, 61.7, 44.4, 41.8, 33.9, 33.5, 31.9, 28.5. IR (neat): 2925, 1751, 1687 cm^{-1}. ESI-MS (ES$^+$): 299 [M+H]$^+$.

*4.4. 3-(2-(piperidin-4-yl)ethyl)oxazolidin-2-one (**13**).*

A solution of **12** (820 mg, 2.7 mmol) in 10 mL 2.2 M HCl/isopropanol was stirred overnight at room temp. The reaction was quenched by the addition of 20 mL 5% NaOH. Brine (20 mL) was added and the aqueous phase was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The residual oil which crystallized spontaneously was then used without further purification (443 mg, 82%). ^{1}H-NMR ($CDCl_3$): δ 4.35 (t, J = 7.9 Hz, 2H), 3.57 (t, J = 7.9 Hz, 2H), 3.35 (t, J = 7.3 Hz, 2H), 3.11−3.06 (m, 2H), 2.71 (td, J = 12.1 Hz, J = 2.2 Hz, 2H), 1.73 (br. s., 3H), 1.52 (q, J = 7.1 Hz, 2H), 1.45−1.37 (m, 1H), 1.22−1.09 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 158.4, 77.3, 61.6, 44.4, 41.8, 34.5, 33.7, 33.2. IR (neat): 3429, 2922, 1741 cm^{-1}. ESI-MS (ES$^+$): 199 [M+H]$^+$.

*4.5. 3-fluoro-4-(oxiran-2-ylmethoxy)benzonitrile (**14**).*

At 0 °C and under N_2, PPh_3 (684 mg, 1.2 equiv.), (*R*)-glycidol (174 µL, 1.2 equiv.) and DIAD (510 µL, 1.2 equiv.) were added to a solution of 3-fluoro-4-hydroxybenzonitrile **7** (300 mg, 2.18

mmol, 1.0 equiv.) in 10 mL anhydrous THF. The solution was warmed to room temp and stirred for 2 h. The reaction was then quenched with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude mixture was purified by flash chromatography (CH_2Cl_2) to afford compound **14** (413 mg, 98%). ^{1}H-NMR ($CDCl_3$): δ 7.44 (dd, J = 8.6 Hz, J = 1.7 Hz, 1H), 7.40 (dd, $J_{H\text{-}F}$ = 10.4 Hz, J = 1.7 Hz, 1H), 7.09 (t, J = 8.6 Hz, $J_{H\text{-}F}$ = 8.6 Hz, 1H), 4.45 (dd, J = 11.4 Hz, J = 2.7 Hz, 1H), 4.08 (dd, J = 11.4 Hz, J = 5.9 Hz, 1H), 3.43−3.39 (m, 1H), 2.97 (t, J = 4.5 Hz, 1H), 2.81 (dd, J = 4.5 Hz, J = 2.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ 153.1 (d, $J_{C\text{-}F}$ = 250 Hz), 150.6 (d, $J_{C\text{-}F}$ = 9.2 Hz), 129.7 (d, $J_{C\text{-}F}$ = 3.1 Hz), 120.0 (d, $J_{C\text{-}F}$ = 21.5 Hz), 117.8, 115.2 (d, $J_{C\text{-}F}$ = 3.1 Hz), 104.7 (d, $J_{C\text{-}F}$ = 9.2 Hz), 70.2, 49.7, 44.4. IR (neat): 3059, 2233 cm^{-1}. ESI-MS (ES$^+$): 194 [M+H]$^+$.

*4.6. (*S*)-3-fluoro-4-(2-hydroxy-3-(4-(2-(2-oxooxazolidin-3-yl)ethyl)piperidin-1-yl)propoxy)benzonitrile (**6**).*

At room temp and under N_2, piperidine **13** (40 mg, 1.0 equiv.) was added to compound **14** (39 mg, 0.2 mmol, 1.0 equiv.) in 1 mL anhydrous THF. The reaction mixture was heated to 50 °C overnight. Solvents were evaporated under vacuum and the crude was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1 to 90:10) to afford compound **6** as a white solid (62 mg, 81%). ^{1}H-NMR ($CDCl_3$): δ 7.43 (dd, J = 8.6 Hz, J = 1.7 Hz, 1H), 7.40 (dd, $J_{H\text{-}F}$ = 10.4 Hz, J = 1.7 Hz, 1H), 7.09 (t, J = 8.6 Hz, $J_{H\text{-}F}$ = 8.6 Hz, 1H), 4.35 (t, J = 8.2 Hz, 2H), 4.15−4.10 (m, 3H), 3.57 (t, J = 8.2 Hz, 2H), 3.34 (t, J = 7.3 Hz, 2H), 3.01 (d, J = 11.3 Hz, 1H), 2.85 (d, J = 11.3 Hz, 1H), 2.56−2.49 (m, 2H), 2.33 (td, J = 9.7 Hz, J = 1.6 Hz, 1H), 2.02 (td, J = 9.7 Hz, J = 2.2 Hz, 1H), 1.78 (d, J = 9.7 Hz, 2H), 1.52 (q, J = 7.0 Hz, 2H), 1.37−1.25 (m, 3H). ^{13}C-NMR ($CDCl_3$): δ 158.4, 152.0 (d, $J_{C\text{-}F}$ = 251 Hz), 151.2 (d, $J_{C\text{-}F}$ = 10.7 Hz), 129.6 (d, $J_{C\text{-}F}$ = 4.6 Hz), 119.8 (d, $J_{C\text{-}F}$ = 21.4 Hz), 117.8 (d, $J_{C\text{-}F}$ = 3.7 Hz), 115.1, 104.3, 77.3, 71.8, 65.2, 61.6, 60.2, 44.4, 41.9, 33.8, 33.1, 32.4. IR (neat): 3421, 2229, 1746 cm^{-1}. ESI-MS (ES$^+$): 392 [M+H]$^+$. Chiral HPLC: (Chiralpak AD 150 × 4.6 mm, hexane/ethanol 40/60, flow rate: 1 mL min^{-1}, detection at 220 nm) t_{major} = 11.7 min, t_{minor} = 13.7 min, 98% ee.

*4.7. (*R*)-4-(2,3-dihydroxypropoxy)-3-hydroxybenzonitrile (**16**).*

Under N_2, (*S*)-isopropylidene glycerol (330 µL, 1.2 equiv.) and *t*BuOK (560 mg, 2.3 equiv.) were added to a solution of 4-fluoro-3-hydroxybenzonitrile **9** (300 mg, 2.15 mmol, 1.0 equiv.) in 1 mL anhydrous DMF. The suspension was heated at 150 °C for 3 h. After cooling to 70 °C, 4 mL 5 M HCl were added and the reaction was cooled down to room temp. The mixture was diluted with 5 mL H_2O and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1 to 90:10) to afford compound **16** (323 mg, 72%). ^{1}H-NMR (DMSO-d_6): δ 7.25 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 7.15 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 4.99 (d, J = 5.4 Hz, 1H), 4.70 (d, J = 5.4 Hz, 1H), 4.09 (dd, J = 9.9 Hz, J = 3.8 Hz, 1H), 3.92 (dd, J = 9.9 Hz, J = 6.2 Hz, 1H), 3.85−3.81 (m, 1H). ^{13}C-NMR (DMSO-d_6): δ 151.6, 147.5, 152.2, 119.7, 118.4, 113.8, 103.2, 70.9, 70.2, 62.8. IR (neat): 3432, 3341, 2941, 2230 cm^{-1}. $[\alpha]_D$ +28.3 (c 0.57, EtOH). ESI-MS (ES$^+$): 210 [M+H]$^+$.

*4.8. (S)-4-(3-bromo-2-hydroxypropoxy)-3-hydroxybenzonitrile (**17**).*

Under N_2, PPh_3 (626 mg, 2.5 equiv.) and CBr_4 (785 mg, 2.5 equiv.) were added to a solution of **16** (200 mg, 0.95 mmol, 1.0 equiv.) in 5 mL CH_2Cl_2. The solution was stirred at room temp for 2 h. The reaction was then quenched with 5 mL 1 M HCl and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by flash chromatography (EtOAc/cyclohex, 1:9 to 1:1) to afford compound **17** (230 mg, 89%). ^{1}H-NMR ($CDCl_3$): δ 7.53 (br. s, 1H), 7.22−7.18 (m, 2H), 6.92 (d, J = 8.9 Hz, 1H), 4.44−4.31 (m, 1H), 4.29−4.19 (m, 2H), 3.67−3.57 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ 149.5, 146.4, 125.4, 119.0, 118.9, 112.7, 105.4, 70.6, 69.5, 33.6. IR (neat): 3455, 3246, 2937, 2245, 1521 cm^{-1}. $[\alpha]_D$ +0.8 (c 0.54, CH_2Cl_2). ESI-MS (ES$^+$): 272.0-274.0 [M+H]$^+$.

*4.9. (*R*)-3-(bromomethyl)-2,3-dihydrobenzo[1,4]dioxine-6-carbonitrile (**8**).*

PPh_3 (86 mg, 1.2 equiv.) and DIAD (65 µL, 1.2 equiv.) were added dropwise at 0 °C to a solution of **17** (75 mg, 0.27 mmol, 1 equiv.) in 2.7 mL anhydrous THF. The solution was stirred for 2 h at room temp. Solvents were evaporated under vacuum and the crude was purified by flash chromatography (CH_2Cl_2). Compound **8** was isolated as a white solid (59 mg, 80%). ^{1}H-NMR ($CDCl_3$): δ 7.25−7.16 (m, 2H), 6.98 (d, J = 8.4 Hz, 1H), 4.49−4.42 (m, 2H), 4.25 (dd, J = 11.9 Hz, J = 6.8 Hz, 1H), 3.60 (dd, J = 10.9 Hz, J = 4.9 Hz, 1H), 3.51 (dd, J = 10.9 Hz, J = 7.1 Hz, 1H). ^{13}C-NMR ($CDCl_3$): δ 147.0, 142.7, 126.4, 121.3, 118.6, 118.2, 105.2, 71.9, 66.1, 28.1. IR (neat): 2935, 2217 cm^{-1}. $[\alpha]_D$ +8.5 (c 0.52, CH_2Cl_2).

*4.10. F17807 (**5**).*[5]

Under N_2, K_2CO_3 (21 mg, 1.5 equiv.) was added to a solution of **8** (26 mg, 0.104 mmol, 1 equiv.) and piperidine **13** (23 mg, 1.1 equiv.) in 1 mL methyl isobutyl ketone. The reaction mixture was heated at 110 °C for 5 h. The reaction was then quenched with 5 mL 1 M HCl and extracted with 5 mL Et_2O. The aqueous layer was basified with NaOH 20% and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude was purified by flash chromatography (CH_2Cl_2/MeOH, 99:1 to 90:10) to afford F17807 **5** as a solid (26 mg, 58%). ^{1}H-NMR ($CDCl_3$): δ 7.18 (d, J = 1.6 Hz, 1H), 7.14 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 4.40−4.28 (m, 4H), 4.03 (dd, J = 11.4 Hz, J = 7.3 Hz, 1H), 3.57 (t, J = 8.2 Hz, 2H), 3.32 (t, J = 7.3 Hz, 2H), 2.97 (d, J = 9.2 Hz, 1H), 2.89 (d, J = 9.2 Hz, 1H), 2.67 (dd, J = 13.3 Hz, J = 5.7 Hz, 1H), 2.55 (dd, J = 13.3 Hz, J = 6.3 Hz, 1H), 2.19−2.06 (m, 2H), 1.74 (d, J = 8.3 Hz, 2H), 1.51 (q, J = 7.0 Hz, 2H), 1.37−1.25 (m, 3H). ^{13}C-NMR ($CDCl_3$): δ 158.4, 147.5, 143.4, 125.8, 121.3, 118.9, 115.0, 104.5, 71.5, 67.3, 61.7, 58.6, 54.2, 44.4, 41.9, 33.8, 32.9, 32.2. IR (neat): 2923, 2224, 1748 cm^{-1}. $[\alpha]_D$ +28.3 (c 0.50, CH_2Cl_2). ESI-MS (ES$^+$): 372 [M+H]$^+$. Chiral HPLC: (Chiralpak AD 150 × 4.6 mm, hexane/ethanol 40:60, flow rate: 1 mL min^{-1}, detection at 220 nm) t_{major} = 11.4 min, t_{minor} = 13.5 min, 98% ee.

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References and notes

1. Lee, D. Y. W.; Liu, Y. *J. Nat. Prod.* **2003**, *66*, 1171.
2. Pallavicini, M.; Budriesi, R.; Fumagalli, L.; Ioan, P.; Chiarini, A.; Bolchi, C.; Ugenti, M. P.; Colleoni, S.; Gobbi M.; Valoti, E. *J. Med. Chem.* **2006**, *49*, 7140.
3. (a) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49. (b) Rouf, A.; Aga, M. A.; Kumar, B.; Taneja, S. C. *Tetrahedron Lett.* **2013**, *54*, 6420.
4. Halliday, C. A.; Jones, B. J.; Skingle, M.; Walsh, D. M.; Wise, H.; Tyers, M. B. *Br. J. Pharmacol.* **1991**, *102*, 887.
5. Sokoloff, P.; Maillos, P.; Cuisiat, F.; Vidaluc, J. L.; Imbert, T. WO patent 106660 (2014).
6. Moureu, C. *Bull. Soc. Chim. Paris*, Mémoires 1899, SER3, T21, 291.
7. Koo, J.; Avakian, S.; Martin, J. G. *J. Am. Chem. Soc.* **1955**, *77*, 5373.
8. Martin, A. R.; Mallick, S. K.; Caputo, J. F. *J. Org. Chem.* **1974**, *39*, 1808.
9. Krapcho J.; Lott, W. A. US patent 2979511 (1961).
10. Ilić, M.; Dunkel, P.; Ilaš, J.; Chabielska, E.; Zakrzeska, A.; Mátyus P.; Kikelj, D. *Eur. J. Med. Chem.* **2013**, *62*, 329.
11. Willard, A. K.; Smith, R. L.; Cragoe, E. J. *J. Org. Chem.* **1981**, *46*, 3846.
12. Bao, W.; Liu, Y.; Lv X.; Quian, W. *Org. Lett.* **2008**, *10*, 3899.
13. Kuwabe, S.; Torraca K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.
14. Bolchi, C.; Fumagalli, L.; Moroni, B.; Pallavicini M.; Valoti, E. *Tetrahedron: Asymmetry* **2003**, *14*, 3779.
15. Rouf, A.; Gupta, P.; Aga, M. A.; Kumar, B.; Chaubey, A.; Parshad, R.; Taneja, S. C. *Tetrahedron: Asymmetry* **2012**, *23*, 1615.
16. Lo Monte, F.; Kramer, T.; Gu, J.; Anumala, U. R.; Marinelli, L.; La Pietra, V.; Novellino, E.; Franco, B.; Demedts, D.; Van Leuven, F.; Fuertes, A.; Dominguez, J. M.; Plotkin, B.; Eldar-Finkelman, H.; Schmidt, B. *J. Med. Chem.* **2012**, *55*, 4407.
17. Massacret, M.; Lakhmiri, R.; Lhoste, P.; Nguefack, C.; Ben Abdelouahab, F. B.; Fadel, R.; Sinou, D. *Tetrahedron: Asymmetry* **2000**, *11*, 3561.
18. Clark, R.; Kurz, L. *Heterocycles* **1985**, *23*, 2005.
19. (a) Hardouin, C.; Doris, E.; Rousseau, B.; Mioskowski, C.; Nierlich, M. *Acta Crystallogr. Sect. C* **2000**, *56*, 225. (b) Hardouin, C.; Doris, E.; Rousseau, B.; Mioskowski, C. *Org. Lett.* **2002**, *4*, 1151. (c) Hardouin, C.; Doris, E.; Rousseau, B.; Mioskowski, C. *J. Org. Chem.* **2002**, *67*, 6571. (d) Hardouin, C.; Burgaud, L.; Valleix, A.; Doris, E. *Tetrahedron Lett.* **2003**, *44*, 435. (e) Moisan, L.; Doris, E.; Rousseau, B.; Thuéry, P. *Acta Crystallogr. Sect. C* **2004**, *60*, o792. (f) Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 5334. (g) Doris, E. *Angew. Chem. Int. Ed.* **2009**, *48*, 7480. (h) Leroux, S.; Larquetoux, L.; Nicolas, M.; Doris, E. *Org. Lett.* **2011**, *13*, 3549. (i) Giovanelli, E.; Leroux, S.; Moisan, L.; Carreyre, H.; Thuéry, P.; Buisson, D. A.; Meddour, A.; Coustard, J. M.; Thibaudeau, S.; Rousseau, B.; Nicolas, M.; Hellier, P.; Doris, E. *Org. Lett.* **2011**, *13*, 4116. (j) Alliot, J.; Gravel, E.; Pillon, F.; Buisson, D. A.; Nicolas, M.; Doris. E. *Chem. Commun.* **2012**, *48*, 8111. (k) Giovanelli, E.; Moisan, L.; Leroux, S.; Comesse, S.; Rousseau, B.; Hellier, P.; Nicolas, M.; Doris, E. *Chem. Eur. J.* **2013**, *19*, 1170. (l) Giovanelli, E.; Moisan, L.; Comesse, S.; Leroux, S.; Rousseau, B.; Hellier, P.; Nicolas, M.; Doris, E. *Org. Biomol. Chem.* **2013**, *11*, 5885. (m) Alliot, J.; Gravel, E.; Larquetoux, L.; Nicolas, M.; Doris, E. *J. Nat. Prod.* **2013**, *76*, 2346. (n) Doris, E. *Angew. Chem. Int. Ed.* **2014**, *53*, 4041.
20. Bollini, M.; Domaoal, R. A.; Thakur, V. V.; Gallardo-Macias, R.; Spasov, K. A.; Anderson, K. S.; Jorgensen, W. L. *J. Med. Chem.* **2011**, *54*, 8582.