Synthesis of LY503430 by using a selective rearrangement of β-amino alcohols induced by DAST

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Dedicated to Professor Pierre Vogel on the occasion of his 70th birthday

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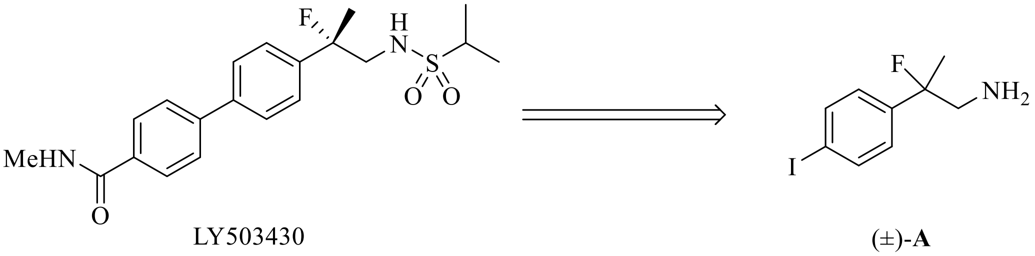
Abstract
LY503430, an optically active β-fluoroamine, is a potential therapeutic agent for the Parkinson's disease. Different strategies have been studied to synthesize this molecule using a regioselective and stereospecific rearrangement of β-amino alcohols into β-fluoroamines induced by DAST. This reaction allowed the synthesis of LY503430 with an excellent enantiomeric excess.

Keywords: Rearrangement, β-amino alcohols, DAST, β-fluoroamines, LY503430

Introduction

LY503430, an optically active β-fluoroamine, which is a potential therapeutic agent for the Parkinson's disease,[1] has been prepared by Eli Lilly on gram scale[2] as well as on a kilogram scale[2] from racemic β-fluoroamine (±)-**A**. The two enantiomers of **A** were separated by using chiral chromatography or diastereomeric salt resolution (Scheme 1).



Scheme 1. Retrosynthesis analysis of LY503430 by Eli Lilly.

Recently, we have reported that *N*,*N*-dialkyl β-amino alcohols **B** can be enantioselectively and regioselectively rearranged to β-fluoroamines **C** by treatment with *N*,*N*-diethylaminosulfur trifluoride (DAST)[3] in excellent yield and enantiomeric excess (Scheme 2).[4]

B **C**

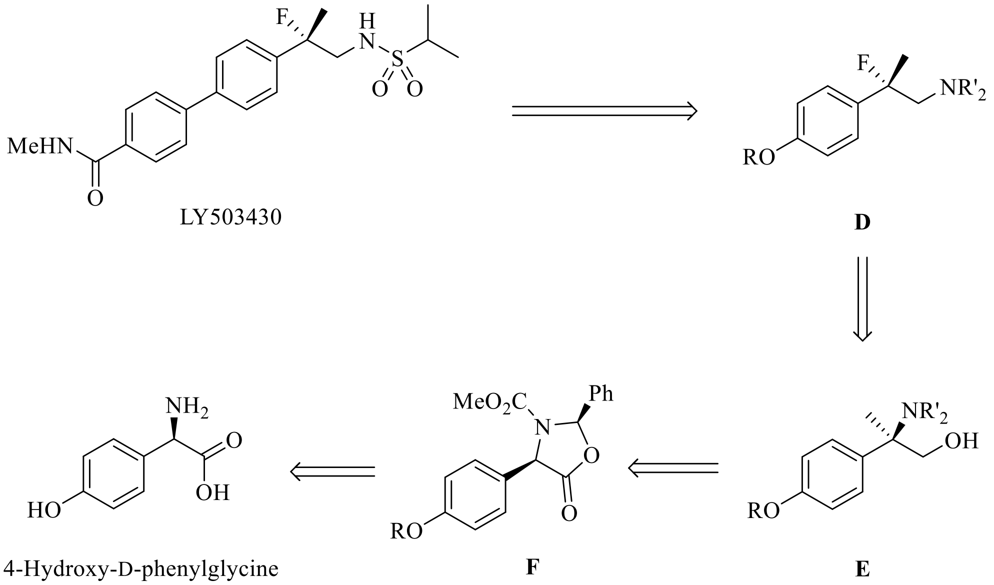
Scheme 2. Stereospecific rearrangement of β-amino alcohols **B** to fluoroamines **C**.

Here, we would like to report our synthetic efforts toward the synthesis of LY503430 by considering the rearrangement of β-amino alcohols **B** as the key step to introduce the β-fluoroamino moiety present in LY503430. Our efforts have culminated to the total synthesis of this biologically active compound.[4]

Results and Discussion

First strategy

Our first synthetic strategy relies on a very late Suzuki cross-coupling of triflate **D** with a boronic acid to produce the biarylic substituent present in LY503430. The synthesis of β-fluoroamine **D** has been envisaged by utilizing an enantioselective rearrangement of β-amino alcohol **E** induced by DAST. A diastereoselective alkylation of **F** was chosen to control the quaternary stereocenter present in **E** and the synthesis of **F** was planned from 4-hydroxy-D-phenylglycine (Scheme 3).

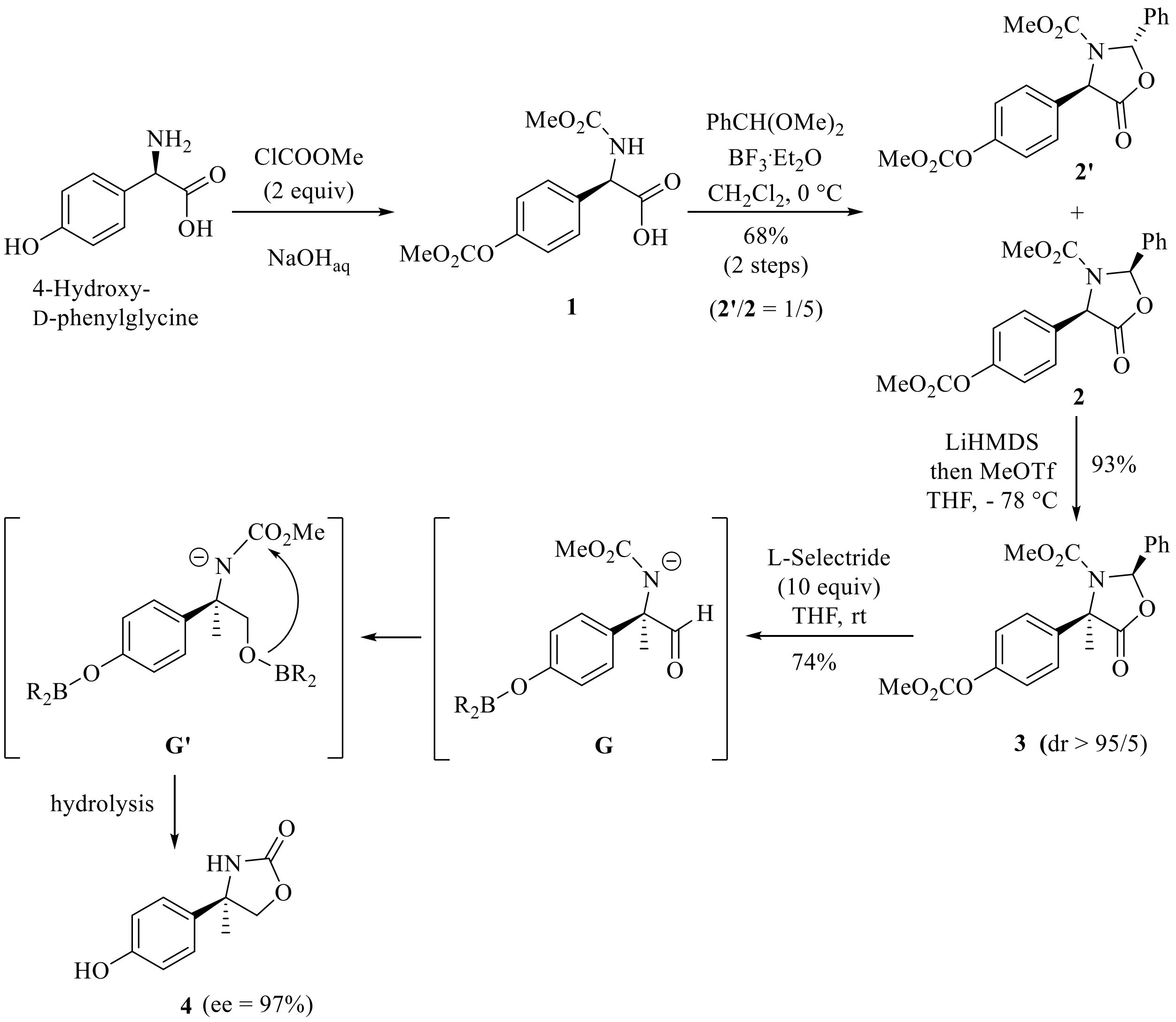


Scheme 3. First retrosynthesis analysis of LY503430.

The synthesis of LY503430 started with the preparation of oxazolidinone **4** in four steps (Scheme 4). 4-Hydroxy-D-phenylglycine was treated with two equivalents of methylchloroformate (NaOH/H_2O) to furnish carbamate **1** and this carbamate was then transformed to a mixture of oxazolidinones **2** and **2'** in a ratio of 5/1, by using benzaldehyde dimethyl acetal under acidic conditions ($BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C).[5] These two diastereoisomers were separated by chromatography on silica gel and compound **2** was isolated with an overall yield of 55% for the two steps. To control the quaternary center present in **4**, oxazolidinone **2** was methylated. Depending on the conditions, the yield in **3** varied from 30% to 93%. Indeed, when **2** was treated with LDA (THF, – 78 °C) followed by the addition of MeI, a degradation of the starting material was observed. The yield in **3** was improved to 31% when LDA was replaced by LiHMDS (THF, – 78 °C) utilizing methyl iodide as the alkylating agent. When methyl iodide was replaced by methyl triflate, the yield in **3** reached 93% and the diastereoselectivity was up to 95/5. After reduction of **3** by L-selectride (10 equiv, THF, rt), oxazolidine **4** was formed in 74% yield, probably *via* intermediate **G** and **G'** (Scheme 4).

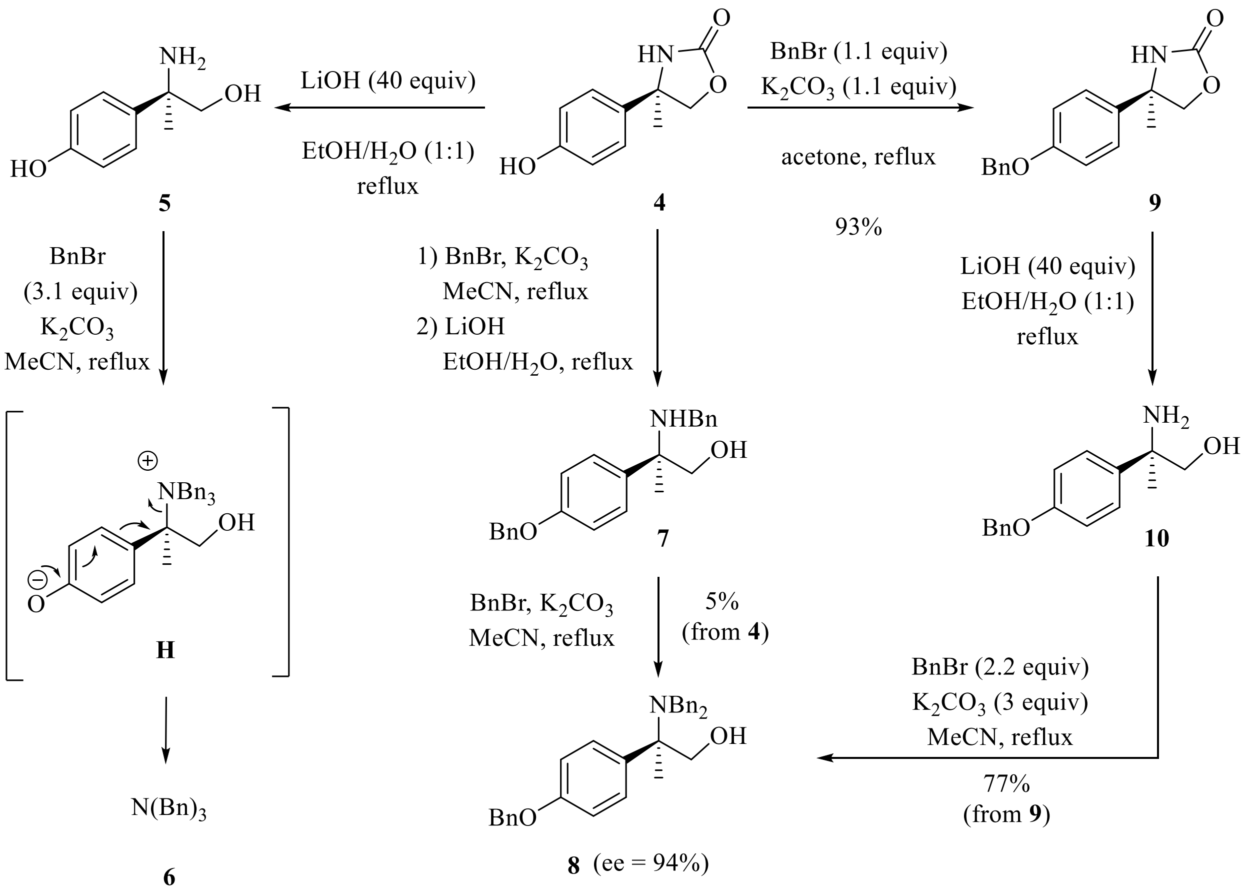
In order to obtain compound **8**, the protected amino alcohol **4** was saponified (LiOH, EtOH/H_2O 1:1, reflux) and a *N*,*N*-dibenzylation as well as the *O*-benzylation were tried [BnBr (3.1 equiv), K_2CO_3, acetone, reflux]. Unfortunately, the desired amino alcohol **8** was not formed but instead tribenzylamine **6** was isolated, probably due to the formation of a tribenzylammonium phenolate intermediate **H** which has the propensity to eliminate the ammonium group (Scheme 5). To avoid this elimination, compound **4** was *N*- and *O*-benzylated (BnBr, K_2CO_3, MeCN, reflux) and then treated with LiOH (aqueous EtOH) to furnish **7** which after *N*-benzylation afforded the desired amino alcohol **8**, however in a very poor yield, e.g. 5% over the three steps due to the poor conversion of oxazolidinone ($\tau_c = 15\%$) to produce **7** during the saponification step. As the non-protection of the phenol functionnality in one hand, and the protection of the amine on the other hand, revealed to be problematic during the transformation of oxazolidinone **4** to amino alcohol **8**, we decided to prepare the protected oxazolidinone **9**. Thus, **4** was selectively *O*-benzylated (BnBr, K_2CO_3, acetone, reflux), and the resulting oxazolidinone **9** (93%) was treated with LiOH to produce amino alcohol **10** with a total conversion. Finally, after *N*,*N*-dibenzylation of **10** (K_2CO_3, BnBr, MeCN, reflux), the desired amino alcohol **8** was isolated in 77% yield over the last two steps with an enantiomeric excess of 94% (Scheme 5).

The key intermediate in the synthesis of LY503430, amino alcohol **8** (ee 94%), was then submitted to DAST to produce β-fluoroamine **11** in 99% yield (Scheme 6). However, each attempt to purify **11** either on silica gel or alumina resulted in its degradation. Furthermore, a partial racemization occured during the process as the enantiomeric excess of **11** revealed to be only 24%. This racemization can be explained by the participation of the electronically enriched benzylated phenol group to the opening of an aziridinium intermediate,[6] intermediate **I**, formed after activation of the hydroxy group of amino alcohol **8** by DAST. Thus, the racemization proceeds probably through the formation of the achiral intermediate **J** (Scheme 6).

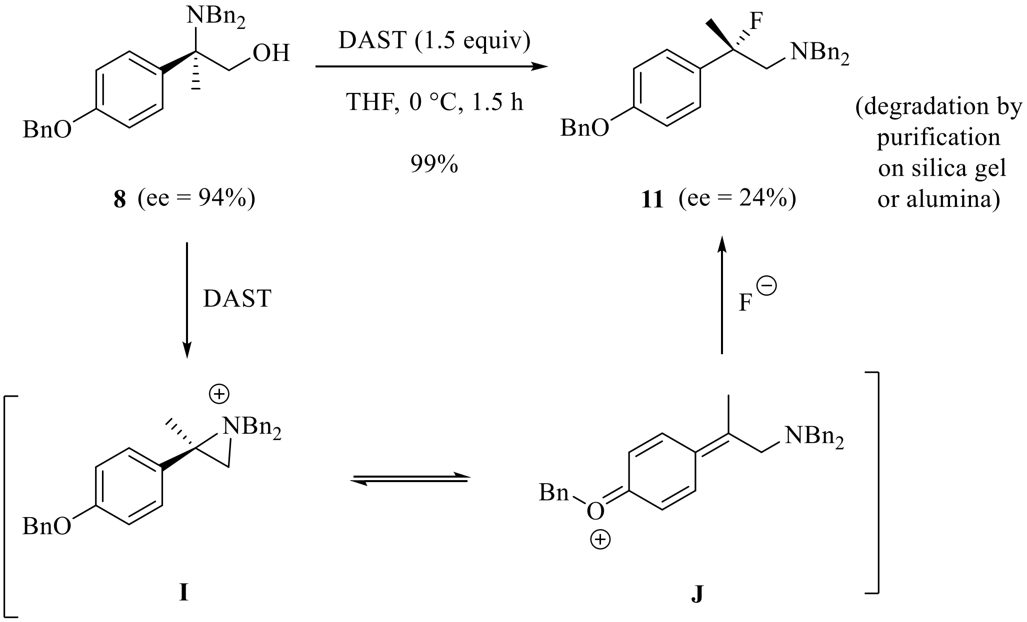


Scheme 4. Synthesis of oxazolidinone **4**

Due to the difficulties encountered to access *β*-fluoroamine **11** with good enantiomeric excess related to the racemization occurring during the rearrangement of amino alcohol **8** induced by DAST, a second strategy was planned to synthesize LY503430.



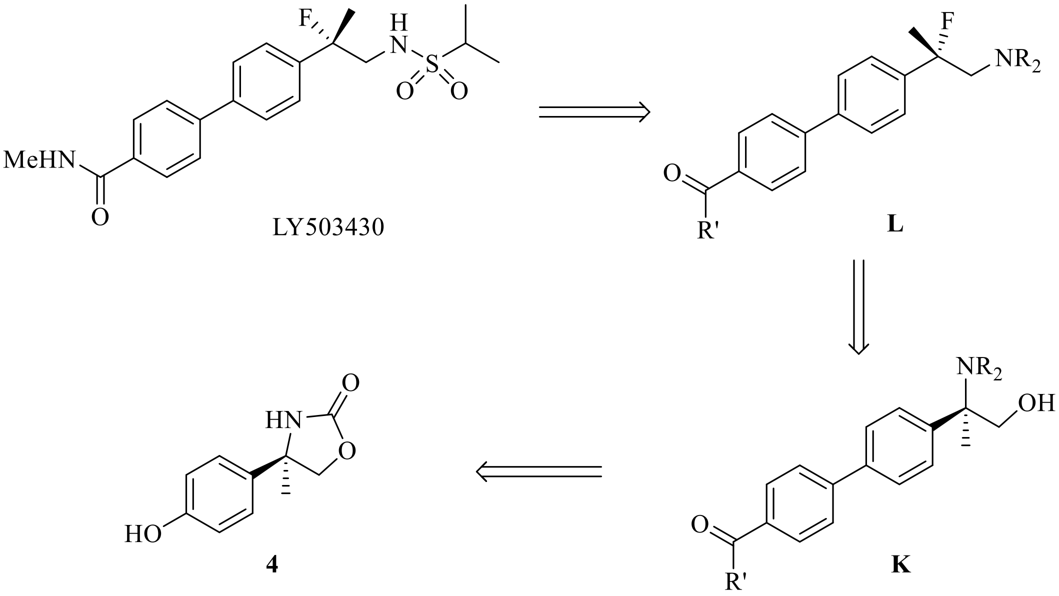
Scheme 5. Synthesis of β-amino alcohol **8**.



Scheme 6. Synthesis of β-fluoroamine **11**.

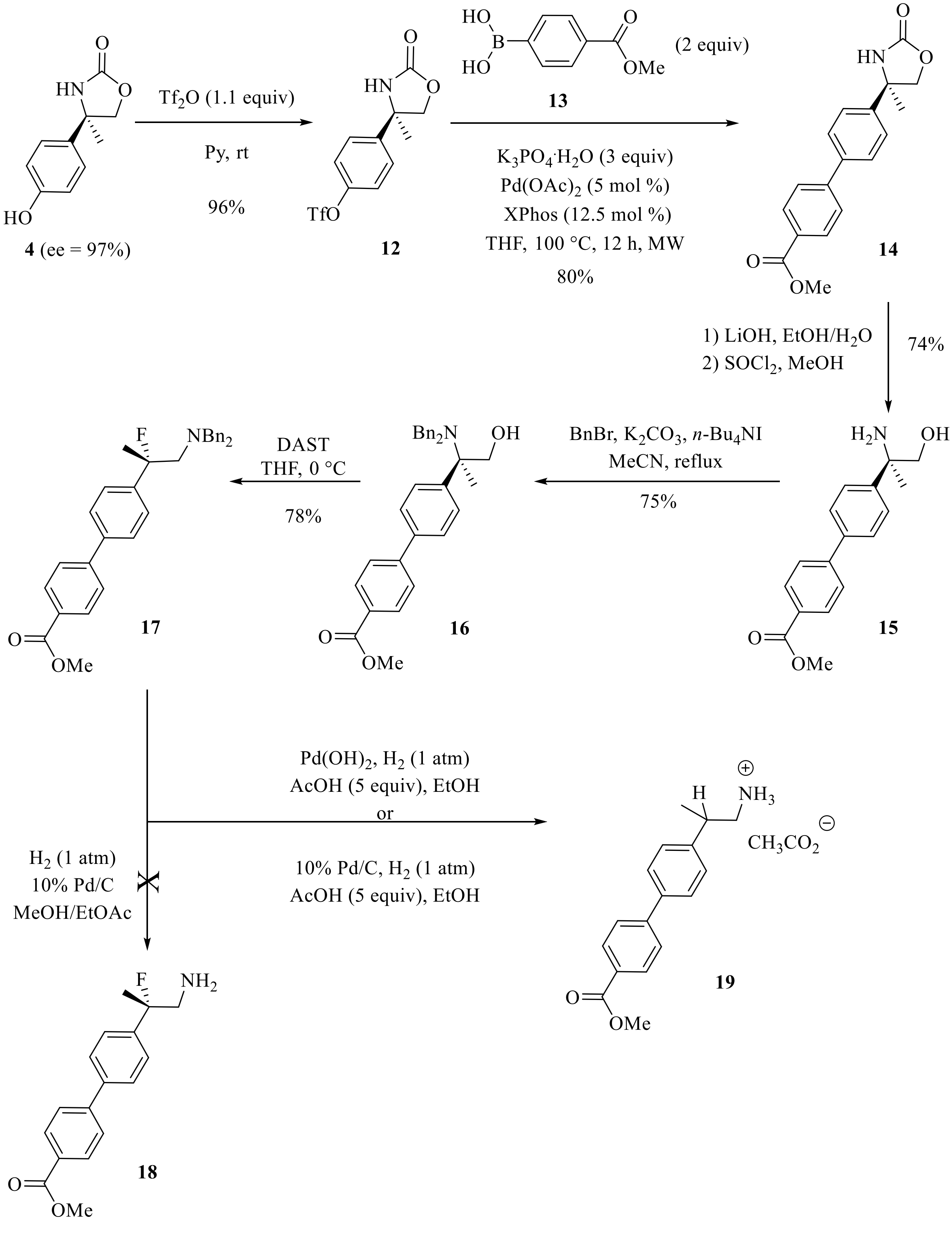
Second strategy

To avoid the racemization during the rearrangement of an amino alcohol by DAST, the synthesis of LY503430 was envisaged by introducing the biphenyl group, possessing an electron-withdrawing substituent, in an early stage of the synthesis of LY503430, before applying the rearrangement induced by DAST. Thus, **4** would be transformed to **K** which would be rearranged to **L**, precursor of LY503430 (Scheme 7).



Scheme 7. Second retrosynthesis analysis of LY503430.

N,*N*-Dibenzyl amino alcohol **16** (compound of type **K**) was synthesized in four steps. At first, oxazolidinone **4** (ee 97%) was transformed to the corresponding triflate **12** (Tf_2O, Py, rt) and after a Suzuki coupling with boronic acid **13** [$K_3PO_4 \bullet H_2O$ (3 equiv), $Pd(OAc)_2$ (5 mol %), XPhos (12.5 mol %), THF, 100 °C, 12 h, MW][7] the biarylic derivative **14** was produced. After treatment of **14** with LiOH and esterification of the formed carboxylic acid ($SOCl_2$, MeOH), the obtained methyl ester **15** was *N*,*N*-dibenzylated (K_2CO_3, BnBr, *n*-Bu_4NI, MeCN, reflux) to produce **16** in 55% overall yield. Compound **16** was then submitted to DAST (THF, 0 °C) and transformed to the desired *β*-fluoroamine **17** (78%). At this stage, the *N*,*N*-dibenzyl protecting group revealed to be troublesome as its removal using H_2 (1 atm), Pd/C in MeOH/EtOAc did not produce the desired fluoroamine **18** but resulted in the degradation of the starting material. The use of Pd/C or $Pd(OH)_2$ with AcOH (5 equiv) in EtOH led to a complex mixture from which the defluorinated derivative **19** was identified (Scheme 8).

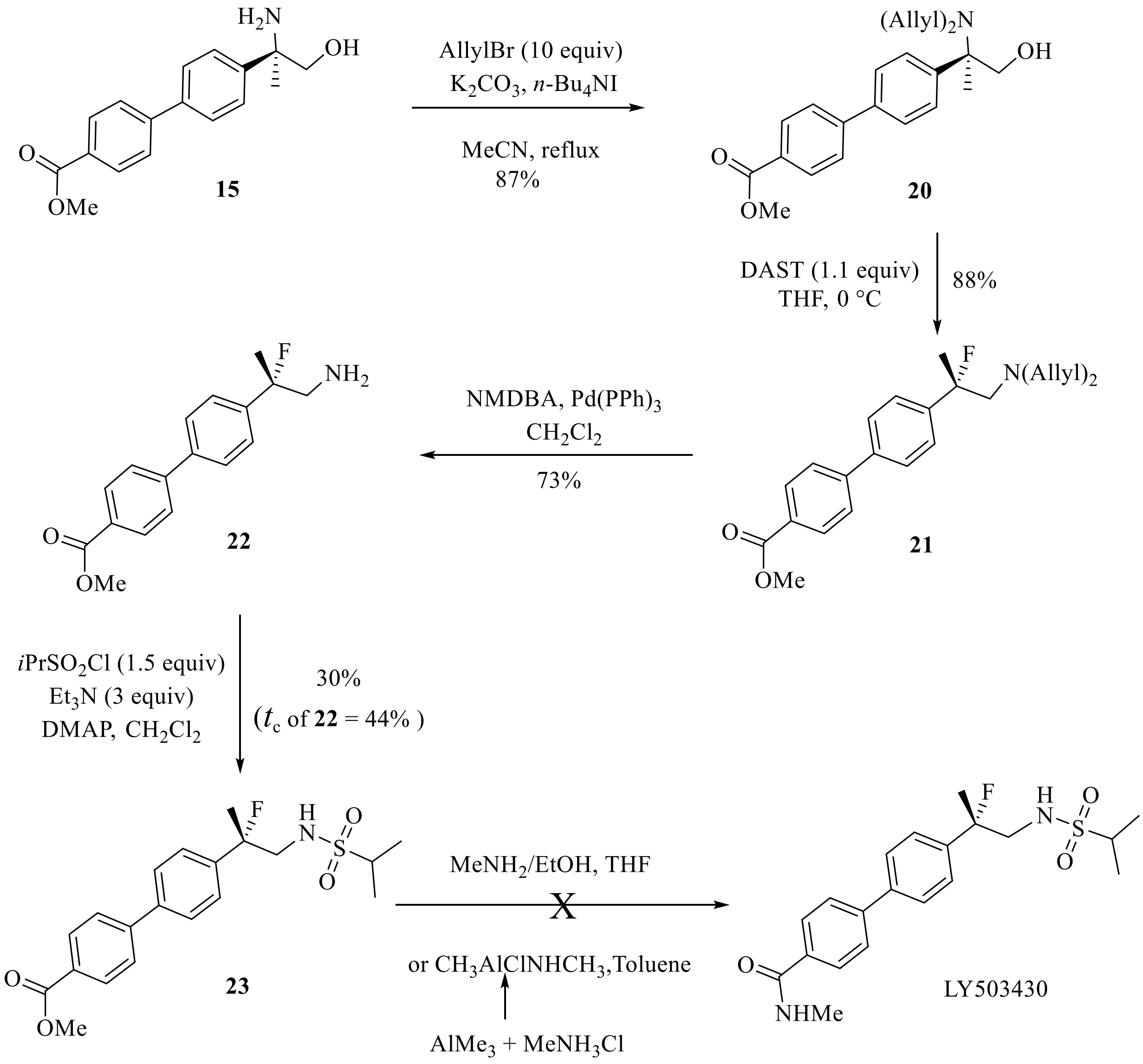


Scheme 8. Synthesis of *β*-fluoroamine **17**.

As the deprotection of the *N*,*N*-dibenzyl group seems to be problematic, the use allyl groups to protect the amino group in **15** was planned. In consequence, β-amino alcohol **15** was transformed to *N*,*N*-diallyl amino alcohol **20** in 87% yield (AllylBr, K_2CO_3, *n*-Bu_4NI, MeCN, reflux). The rearrangement of *N*,*N*-diallyl amino alcohol **20** induced by DAST (1.1 equiv) in THF (0 °C, 1 h) furnished the desired fluoroamine **21** (88%) and the amine was then deprotected by treatment with *N*,*N*-dimethyl barbituric acid (NMDBA) in the presence of $Pd(PPh_3)_4$ in CH_2Cl_2[8] leading to β-fluoroamine **22** (73% yield). To complete the synthesis of LY503430 from **22**, this compound was sulfonylated (*i*-$PrSO_2Cl$ (1.5 equiv), Et_3N (3 equiv), CH_2Cl_2) and the desired sulfonamide **23** was isolated with a moderate yield of 30% due to the limited conversion of **22** ($\tau_c = 44\%$). The last step to obtain LY503430 consisted of the transformation of the ester group in **23** to a methyl amide. A one-step procedure using either $MeNH_2$ in EtOH or MeAlClNHMe (obtained by reaction of $AlMe_3$ with $MeNH_3Cl$)[9] as amidification reagents unfortunately led to the degradation of substrate **23** (Scheme 9).

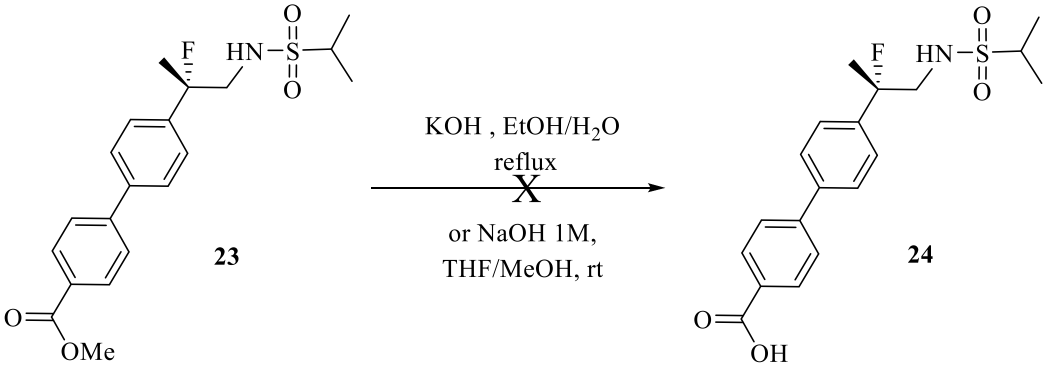
Attempts utilizing a two-step procedure using a saponification followed by an amidification also failed. Indeed neither harsh conditions (KOH, EtOH/H_2O, reflux) nor soft conditions (NaOH 1M, THF/MeOH, rt) led to the desired carboxylic acid **24**. A degradation of the substrate was also observed along with the loss of the fluorine atom (Scheme 10).

As the benzylic position of the fluorine atom seems to decrease the energy of the C-F bond and entailed unwanted degradation, the introduction of the fluorine atom and the methyl amide present in LY503430, were planned at a late stage of the synthesis e.g. from **20**. The transformation of the methyl ester in **20** to a methyl amide was realized in one step using Weinreb's conditions.[9] Treatment of **20** with 2.0 equiv of MeAlClNHMe (obtained by reaction of $AlMe_3$ $MeNH_3Cl$) allowed the transformation of the methyl ester to a *N*-methyl amide, however the replacement of the allylamine by a *N*-methylamine was observed and compound **25** was isolated in 70% yield (Scheme 11). The formation of **25** could result from the activation of the hydroxyl group by MeAlClNHMe to furnish intermediate **26**. The anchimeric assistance of the nitrogen atom associated with the nucleophilic displacement of the MeNH–Al–O moiety could entail an intramolecular rearrangement resulting in the formation of **25** (Scheme 11, route a). This rearrangement could also be the result of the formation of aziridinium **26'** (Scheme 11, route b), similar to the one formed during the rearrangement of amino alcools induced by DAST.[4,10-15]

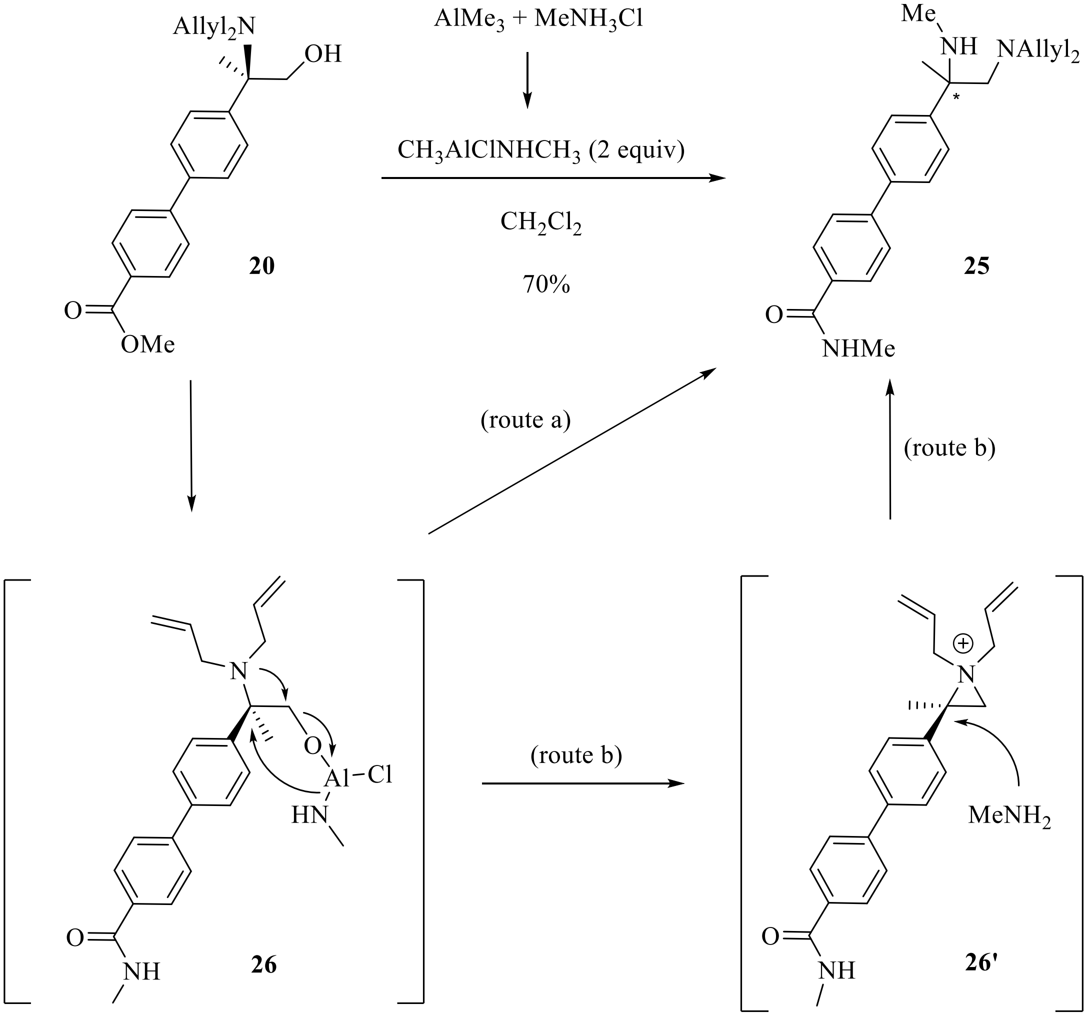


Scheme 9. Synthesis of sulfonamide **23**.

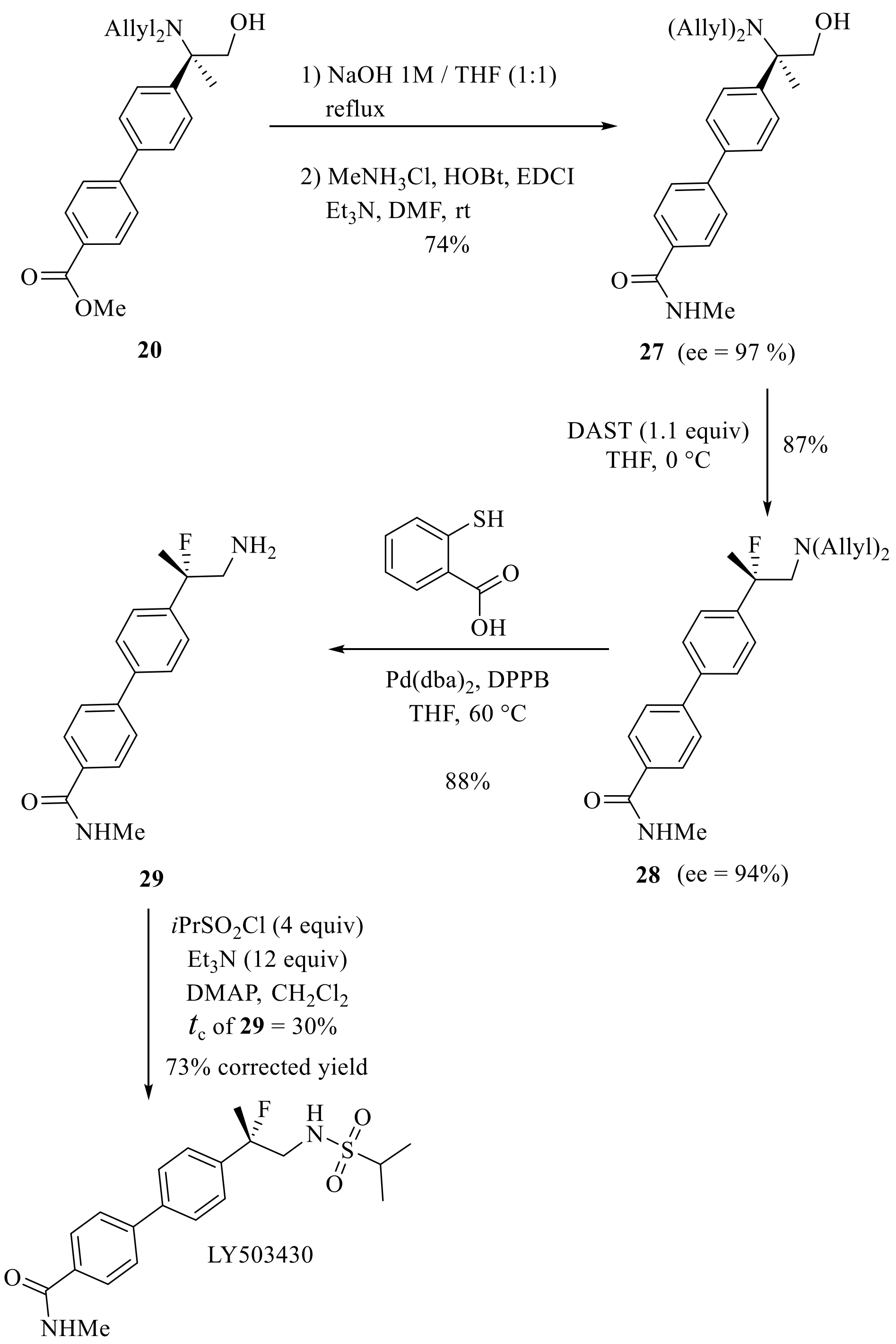
As a consequence, the transformation of **20** to the corresponding amide was realized in two steps. After saponification of the ester group (NaOH 1M/THF=1:1) and amidification of the resulting carboxylic acid ($MeNH_3Cl$, HOBt, EDCI, Et_3N, DMF), compound **27** was isolated in 74% yield and with an enantiomeric excess of 97%. The key rearrangement, to obtain the desired β-fluoroamine, was then performed by treating **27** with DAST (1.1 equiv) in THF (0 °C, 1 h) producing fluoroamine **28** in 87% yield and with an enantiomeric excess of 94%. To complete the synthesis of LY503430, the amino group in **28** was deprotected using $Pd(dba)_2$ in the presence of thiosalicylic acid and 1,4-bis(diphenylphosphino)butane (DPPB) in THF,[16] the resulting amine **29** (88% yield) was then sulfonylated (*i*$PrSO_2Cl$, Et_3N, DMAP, CH_2Cl_2, τ_c of **29** = 30%, corrected yield 73%) producing LY503430 (Scheme 12).[4]



Scheme 10. Saponification test of **23**.



Scheme 11. Synthesis of amide **25**.



Scheme 12. Synthesis of amide LY503430.

The spectroscopic data as well as the αD [αD +27.7, (*c* 0.1, MeOH)] were in perfect agreement with those previously reported in the litterature [αD +31.0, (*c* 1.0, MeOH)].[2]

Conclusion

The synthesis of LY503430 was achieved successfully from 4-hydroxy-D-phenylglycine in 14 steps with an overall yield of 8.1%. The key steps were the construction of the quaternary center through a diastereoselective alkylation, a Suzuki coupling to introduce the biarylic function and the rearrangement induced by DAST to obtain the chiral *β*-fluoroamine moiety.
It is worth noting that this highly enantio- and regioselective rearrangement is sensitive to the nature of the substituents present on the aromatic ring(s) of aryl or *bis*-aryl amino alcohols.

Experimental Section

General. Experimental procedure for the synthesis of compounds **2**, **2'**, **3**, **4**, **12**, **14**, **15**, **20, 27–29** and **LY503430** with copies of their ^{1}H and ^{13}C NMR spectra were previously reported.[4] ^{1}H NMR spectra were recorded on a Bruker AVANCE 400 at 400 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane as internal standard, multiplicity (s = singulet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, integration). ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as internal standard ($CDCl_3$, δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH_2, q = CH_3). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column) -5971 MS (70 eV). Infrared (IR) spectra were recorded on a Bruker TENSOR^{TM} 27 (IRFT), wave-numbers are indicated in cm^{-1}. THF was distilled from sodium-benzophenone. Reagents obtained from commercial suppliers were used as received. TLC was performed on Merck 60F$_{254}$ silica gel plates and visualized with a UV lamp (254 nm), or by using solutions of $KMnO_4$/K_2CO_3/NaOH in water or by using *p*-anisaldehyde/sulfuric acid/acetic acid in EtOH followed by heating. Column chromatography was performed with Merck Geduran Si 60 silica gel (40–63 µm). High resolution mass spectra (HRMS) were performed by the centre regional de microanalyse (Université Pierre et Marie Curie Paris VI).

General procedure for rearrangement of β-aminoalcohols induced by DAST. To a solution of *β*-amino alcohol of type **B** in THF (0.05 M) was added DAST (1.1 to 2.2 equiv) at 0 °C. The mixture was stirred for 1 h at 0 °C and then warmed to rt. After addition of H_2O, the mixture was extracted with twice CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel afforded *β*-fluoroamines of type **C**.

(*R*)-2-(4-(Benzyloxy)phenyl)-2-(*N*,*N*-dibenzylamino)propan-1-ol (8). To a solution of **9** (280 mg, 0.99 mmol, 1.0 equiv) in EtOH/H_2O (10 mL/10 mL) was added LiOH (1 g, 42 mmol, 42 equiv). After 18 h at reflux, EtOH was evaporated and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give **10** (234 mg, 0.91 mmol, 92% crude yield). The residue was dissolved in MeCN (10 mL) and K_2CO_3 (378 mg, 2.73 mmol, 3.0 equiv), *n*-Bu_4NI (100 mg, 0.27 mmol, 0.3 equiv) and BnBr (240 µL, 2.0 mmol, 2.2 equiv) were added. After 6 h at reflux, MeCN was evaporated and the residue was dissolved in H_2O/EtOAc. The aqueous phase was extracted with EtOAc (2 × 20 mL), the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 90/10) afforded **8** (333 mg, 0.76 mmol, 77%) as a colorless oil. $[\alpha]_D^{25}$ + 61.3 (*c* 1.0, $CHCl_3$); IR (neat): 3500–2500, 1605, 1508, 1240, 1025, 828 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* 8.8 Hz, 2H), 7.45–7.11 (m, 15H), 7.01 (d, *J* 8.8 Hz, 2H), 5.06 (s, 2H), 3.70 (d, *J* 14.5 Hz, 2H), 3.62 (d, *J* 14.5 Hz, 2H), 3.50 (d, *J* 11.1 Hz, 1H), 3.46 (d, *J* 11.2 Hz, 1H), 1.54 (s, 3H), 1.43 (br s, 1H, H_{alcool}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9 (s), 141.5 (s, 2C), 137.1 (s), 136.9 (s), 128.7 (d, 2C), 128.6 (d, 2C), 128.5 (d, 4C), 128.2 (d, 4C), 128.0 (d), 127.6 (d, 2C), 126.8 (d, 2C), 114.5 (d, 2C), 70.1 (t), 70.1 (t), 66.1 (s), 54.2 (t, 2C), 15.6 (q); HRMS Calcd for $C_{30}H_{32}NO_2$ ($M+H^+$): 438.2427; Found: 438.2426.

(*R*)-4-(4-(Benzyloxy)phenyl)-4-méthyloxazolidin-2-one (9). To a solution of **4** (520 mg, 2.7 mmol, 1.0 equiv) in acetone (10 mL), were added K_2CO_3 (410 mg, 3.0 mmol, 1.1 equiv) and BnBr (350 µL, 3.0 mmol, 1.1 equiv). After 4 h at reflux, the solution was concentrated under vacuum, the residue was dissolved in EtOAc and a solution of HCl 1M was added. The aqueous phase was extracted with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Crystallisation of the residue in pentane afforded **9** (706 mg, 2.5 mmol, 93%) as a white solid. $[\alpha]_D^{25}$ – 51.9 (*c* 1.0, $CHCl_3$); mp 148–150 °C; IR (neat): 3203, 1762, 1512, 1387, 1245, 1183, 1013, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.26 (m, 7H), 6.98 (d, *J* 9.0 Hz, 2H), 6.27 (s, 1H, H_{amide}), 5.06 (s, 2H), 4.33 (d, *J* 8.4 Hz, 1H), 4.30 (d, *J* 8.3 Hz, 1H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2 (s), 158.4 (s), 136.7 (s), 135.7 (s), 128.7 (d, 2C), 128.1 (d), 127.5 (d, 2C), 126.0 (d, 2C), 115.2 (s, 2C), 78.4 (t), 70.1 (t), 60.0 (s), 27.6 (q). MS-EI *m/z* (%): 283 ($M^{+\bullet}$, 8), 268 (4), 207 (3), 91 (100), 65 (8). HRMS Calcd for $C_{17}H_{17}NaNO_3$ ($M+Na^+$) : 306.1100; Found: 306.1101.

(*S*)-*N*,*N*-Dibenzyl-2-(4-(benzyloxy)phenyl)-2-fluoropropan-1-amine (11). Following the general procedure, amino alcool **8** (100 mg, 0.23mmol, 1.0 equiv) was treated with DAST (45 µL, 0.34 mmol, 1.5 equiv) during 1.5 h at 0 °C, to furnish **11** (99 mg, 0.34 mmol, 99% crude yield). Analyses were realized on the crude residue. IR (neat): 3030, 1674, 1600, 1509, 1453, 1243, 1025, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.11 (m, 15H), 7.10 (d, *J* 8.6 Hz, 2H), 6.90 (d, *J* 8.4 Hz, 2H), 5.06 (s, 2H), 3.72 (br s, 2H), 3.56 (br s, 2H), 2.84 (br s, 2H), 1.59 (d, *J* 23.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0 (s), 139.6 (s), 137.0 (s, 2C), 136.6 (s), 129.0 (d, 2C), 128.6 (d, 4C), 128.2 (d, 4C), 128.0 (d), 127.5 (d, 2C), 126.9 (d, 2C), 125.8 (d, 2C), 114.4 (d, 2C), 99.5 (ds, *J* 200.9 Hz), 70.1 (t), 62.5 (t), 59.5 (t, 2C), 25.3 (qd, *J* 37.5 Hz).

(*R*)-Methyl-4'-(2-(*N*,*N*-Dibenzylamino)-1-hydroxypropan-2-yl) biphenyl-4-carboxylate (16). To a solution of **15** (110 mg, 0.39mmol, 1.0 equiv) in MeCN (5mL) were added K_2CO_3 (160 mg, 1.16mmol, 3.0 equiv), *n*Bu$_4$NI (43 mg, 0.12, 0.3 equiv) and BnBr (101µL, 0.85mmol, 2.2 equiv). After 9 h at reflux, MeCN was evaporated and the residue dissolved in H_2O/EtOAc. The aqueous phase was extracted with EtOAc, the combined organic layers are dried on $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 80/20) afforded **16** (134 mg, 0.29 mmol, 75%) as a colorless oil. $[\alpha]_D^{25}$ + 93.8 (*c* 0.50, $CHCl_3$); IR (neat): 3500–2800, 1704, 1606, 1439, 1281, 1113, 1026, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* 8.0 Hz, 2H), 7.73 (d,*J* 8.8 Hz, 2H), 7.61–7.58 (m, 4H), 7.22–7.06 (m, 10H), 3.86 (s, 3H), 3.67 (d, *J* 14.5 Hz, 2H), 3.61 (d, *J* 14.6 Hz, 2H), 3.51 (d, *J* 11.2 Hz, 1H), 3.46 (d, *J* 10.9 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (s), 145.2 (s), 145.1 (s), 141.3 (s, 2C), 138.7 (s), 130.1 (d, 2C), 128.9 (s), 128.5 (d, 4C), 128.3 (d, 4C), 128.1 (d, 2C), 127.1 (d, 2C), 127.0 (d, 2C), 126.9 (d, 2C), 69.9 (t), 65.5 (s), 54.3 (t, 2C), 52.2 (q), 15.5 (q). MS-EI *m/z* (%): 268 ($M^{+\bullet}$–Bn_2NH, 17), 239 (100), 180 (18), 165 (24), 152 (10), 59 (19). HRMS Calcd for $C_{31}H_{32}NO_3$ ($M+H^+$): 466.2376; Found: 466.2376.

(*S*)-Methyl-4'-(1-(*N*,*N*-Dibenzylamino)-2-fluoropropan-2-yl)biphenyl-4-carboxylate (17). Following the general procedure, amino alcool **16** (52 mg, 0.11mmol, 1.0 equiv) was treated with DAST (18µL, 0.11 mmol, 1.1 equiv) for 1 h at 0 °C, to furnish an oil which was purified by flash chromatography on silica gel (petroleum ether/EtOAc 96/4) to give **17** (41 mg, 0.09mmol, 78%) as a colorless oil. $[\alpha]_D^{25}$ – 84.0 (*c* 1.0, $CHCl_3$); IR (neat): 2926, 1714, 1608, 1431, 1275, 1100, 832 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* 8.8 Hz, 2H), 7.59 (d, *J* 8.5 Hz, 2H), 7.48 (d, *J* 8.0 Hz, 2H), 7.21–7.12 (m, 12H), 3.87 (s, 3H), 3.62 (d, *J* 13.5 Hz, 2H), 3.52 (d, *J* 13.6 Hz, 2H), 2.83 (dd, *J* 28.0, 14.6 Hz, 1H), 2.77 (dd, *J* 29.6, 14.6 Hz, 1H), 1.54 (d, *J* 23.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (s), 145.2 (s), 144.1 (ds, *J* 22.3 Hz), 139.5 (s, 2C), 138.8 (s), 130.2 (d, 2C), 129.1 (d, 4C), 128.9 (s), 128.1 (d, 4C), 127.0 (d, 2C), 126.9 (d, 4C), 125.2 (dd, *J* 9.6 Hz, 2C), 99.5 (ds, *J* 174.3 Hz), 62.3 (dt, *J* 21.7 Hz), 59.5 (dt, *J* 3.6 Hz, 2C), 52.2 (q), 25.5 (dq, *J* 25.0 Hz); HRMS Calcd for $C_{31}H_{31}N_2OF$ ($M+H^+$): 468.2333; Found: 468.2330.

(*S*)-Methyl 4'-(1-(diallylamino)-2-fluoropropan-2-yl)-biphenyl-4-carboxylate (21). Following the general procedure, amino alcool **20** (140 mg, 0.38mmol, 1.0 equiv) was treated with DAST (55µL, 0.42 mmol, 1.0 equiv) for 1 h at 0 °C, to furnish an oil which was purified by flash chromatography on silica gel (petroleum ether/EtOAc 95/5) to give **21** (123 mg, 0.34 mmol, 88%) as a colorless oil. $[\alpha]_D^{25}$ – 5.3 (*c* 1.0, $CHCl_3$); IR (neat): 2950, 1719, 11609, 1434, 1276, 1110, 918, 829, 773 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* 8.5 Hz, 2H), 7.58 (d, *J* 8.5 Hz, 2H), 7.52 (d, *J* 8.3 Hz, 2H), 7.35 (d, *J* 8.5 Hz, 2H), 5.76–5.66 (m, 2H), 5.06–5.01 (m, 4H), 3.85 (s, 3H), 3.14 (dd, *J* 13.8, 5.3 Hz, 2H), 3.00 (dd, *J* 13.7, 6.1 Hz, 2H), 2.83–2.67 (m, 2H), 1.65 (d, *J* 22.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (s), 145.1 (s), 144.2 (ds, *J* 21.5 Hz), 138.9 (s), 135.8 (d, 2C), 130.1 (d, 2C), 129.0 (s), 126.9 (d, 2C), 126.9 (d, 2C), 125.2 (dd, *J* 9.6 Hz, 2C), 117.3 (t, 2C), 98.8 (ds, *J* 174.0 Hz), 62.0 (dt, *J* 23.1 Hz), 58.1 (dt, *J* 2.1 Hz, 2C), 52.0 (q), 24.8 (dq, *J* 24.6 Hz); MS-EI *m/z* (%): 347 ($M^{+\bullet}$–HF, 5), 332 (7), 252 (7), 110 (100), 68 (11); HRMS Calcd for $C_{23}H_{27}FNO_2$ ($M+H^+$) : 368.2020; Found: 368.2022.

(*S*)-Methyl 4'-(1-amino-2-fluoropropan-2-yl)-biphenyl-4-carboxylate (22). To a solution of **21** (123 mg, 0.34 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) were successively added NMDBA

(314 mg, 2.0 mmol, 6.0 equiv) and $Pd(PPh_3)_4$ (40 mg, 0.03 mmol, 0.1 equiv). After 2 h of stirring at 35 °C, the solution was concentrated and the residue dissolved in Et_2O/EtOAc 1:1 (15 mL). The organic phase was washed 5 times with an aqueous saturated solution of Na_2CO_3, dried on Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/MeOH 90/10 + 0.5% Et_3N) afforded **22** (69 mg, 0.24 mmol, 73%) as a yellow oil. $[\alpha]_D^{25}$ + 11.3 (*c* 1.0, CH_2Cl_2); IR (neat): 2948, 1711, 1607, 1442, 1280, 1114, 831, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* 8.4 Hz, 2H), 7.59 (d, *J* 8.4 Hz, 2H), 7.57 (d, *J* 8.4 Hz, 2H), 7.36 (d, *J* 8.4 Hz, 2H), 3.87 (s, 3H), 3.04–2.98 (m, 2H), 1.61 (d, *J* 22.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0 (s), 145.0 (s), 142.7 (ds, *J* 22.1 Hz), 139.2 (s), 130.2 (d, 2C), 129.1 (s), 127.4 (d, 2C), 127.0 (d, 2C), 125.1 (dd, *J* 9.6 Hz, 2C), 98.1 (ds, *J* 172.6 Hz), 52.2 (dt, *J* 24.3 Hz), 52.1 (q), 25.0 (dq, *J* 24.8Hz); HRMS Calcd for $C_{17}H_{19}F\,N\,O_2$ $(M+H^+)$: 288.1394; Found: 288.1397.

(*S*)-Methyl 4'-(2-fluoro-1-(1-methylethylsulfonamido)-propan-2-yl)-biphenyl-4-carboxylate (**23**). To a solution of **22** (22 mg, 0.08 mmol, 1.0 equiv) and Et_3N (33 μL, 0.24 mmol, 3.0 equiv) in CH_2Cl_2 (1 mL) was slowly added at 0 °C *i*-$PrSO_2Cl$ (13 μL, 0.12 mmol, 1.5 equiv). After 18 h of stirring at rt, H_2O was added and the solution extracted with CH_2Cl_2. The organic phase was dried on Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 70/30) afforded **23** (9 mg, 0.023 mmol, 30%) as a white solid. $[\alpha]_D^{25}$ + 25.2 (*c* 0.5, $CHCl_3$) ; mp 148–150 °C ; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* 8.7 Hz, 2H), 7.58 (d, *J* 8.5 Hz, 4H), 7.38 (d, *J* 8.5 Hz, 2H), 4.23 (t, *J* 6.3 Hz, 1H, $H_{sulfonamide}$), 3.88 (s, 3H), 3.61–3.45 (m, 2H), 2.99 (sept, *J* 6.8 Hz, 1H), 1.70 (d, *J* 22.6 Hz, 3H), 1.24 (d, *J* 7.0 Hz, 3H), 1.21 (d, *J* 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (s), 144.7 (s), 141.3 (ds, *J* 21.8 Hz), 139.9 (s), 130.2 (d, 2C), 129.2 (s), 127.5 (d, 2C), 127.0 (d, 2C), 124.9 (dd, *J* 9.5 Hz, 2C), 96.9 (ds, *J* 175.0 Hz), 54.0 (d), 52.6 (dt, *J* 23.2 Hz), 52.2 (q), 24.8 (dq, *J* 24.8 Hz), 16.6 (q), 16.5 (q); MS-EI *m/z* (%): 373 ($M^{+\bullet}$–HF, 46), 342 (8), 266 (100), 237 (37), 207 (30), 191 (14), 178 (43), 152 (20), 59 (41). HRMS Calcd for $C_{20}H_{24}O_4NaFNS$ $(M+Na^+)$: 416.1302; Found: 416.1304.

(*S*)-4'-(1-(*N*,*N*-Diallylamino)-2-(methylamino)propan-2-yl)-*N*-methylbiphenyl-4-carboxamide (25). To a solution of $MeNH_2{\cdot}HCl$ (68 mg, 1 mmol, 1.0 equiv) in toluene (1 mL), was added at 0 °C a solution of $AlMe_3$ 2M in hexane (0.5 mL, 1 mmol, 1.0 equiv). The solution was stirred during 1.5 h at rt until disappearance of gas emission. To a solution of **20** (32 mg, 0.088 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added a solution of MeAlClNHMe 0.67M in toluene previously prepared (260 μL, 0.174 mmol, 2.0 equiv). After 12 h at rt, as no conversion of the starting material was noticed, the solution was stirred under microwave irradiation at 80 °C for 1 h then at 100 °C for 1 h. An aqueous solution of HCl 1M was added to the reaction mixture and the aqueous phase was washed with CH_2Cl_2. The aqueous phase was basified with an aqueous solution of NaOH 2M and extracted with EtOAc. The combined organic layers were dried on $MgSO_4$, filtered and concentrated under reduced pressure to give **25** (23 mg, 0.061 mmol, 70%) as a yellow gum. $[\alpha]_D^{25}$ + 3.3 (*c* 1.0, $CHCl_3$); IR (neat): 3348, 2993, 2799, 1636, 1550, 1492, 1409, 1303, 917 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* 8.3 Hz, 2H), 7.58

(d, *J* 8.3 Hz, 2H), 7.51 (d, *J* 8.5 Hz, 2H), 7.44 (d, *J* 8.5 Hz, 2H), 6.25 (m, 1H, H_{amide}), 5.72–5.62 (m, 2H), 5.01–4.96 (m, 4H), 2.96 (d, *J* 4.6 Hz, 3H), 2.93–2.90 (m, 4H), 2.63 (s, 2H), 2.19 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0 (s), 144.4 (s), 143.7 (s), 138.0 (s), 135.5 (d, 2C), 133.1 (s), 127.5 (d, 2C), 127.4 (d, 2C), 127.0 (d, 2C), 126.8 (d, 2C), 117.3 (t, 2C), 69.2 (t) , 60.6 (s), 58.3 (t, 2C), 29.0 (q), 26.9 (q), 22.0 (q); MS-EI *m/z* (%): 267 ($M^{+\bullet}$–$Allyl_2NHCH_2^{\bullet}$, 100), 251 (4), 209 (9), 152 (5), 110 (76), 56 (83); HRMS Calcd for $C_{24}H_{32}N_3O$ ($M+H^+$): 378.2539.; Found: 378.2541.

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