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Stereoselective Synthesis of Fluorinated 1,3-*cis*-Diaminocyclopentanes

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Abstract

Several fluorinated 1,3-diaminocyclopentanes, previously reported to be useful RNA structural probes, can be prepared in a diastereoselective manner from a single bicyclic hydrazine precursor, in 3 to 9 steps.

The presence of a fluorine atom in a molecule is known to significantly influence its physico-chemical properties.[1] As a result, selective introduction of fluorine atoms into an organic compound is a classical way to tune its biological properties.[2] The great NMR sensitivity of the naturally abundant ^{19}F nucleus can also be exploited to investigate biophysical events using the detection of fluorinated molecular probes.[3] In our ongoing work on the fragment-based design of small molecular RNA binders,[4] we have recently reported that fluorinated diamino cyclopentanes **1** can be useful small external probes to study RNA structures (Scheme 1).[5] Herein, we present how to prepare these compounds in an enantio- and/or diastereoselective manner from bicyclic hydrazine **2** as a single precursor.

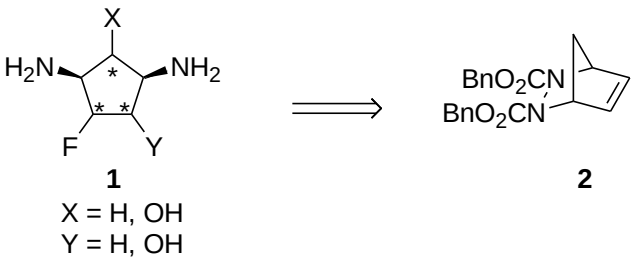
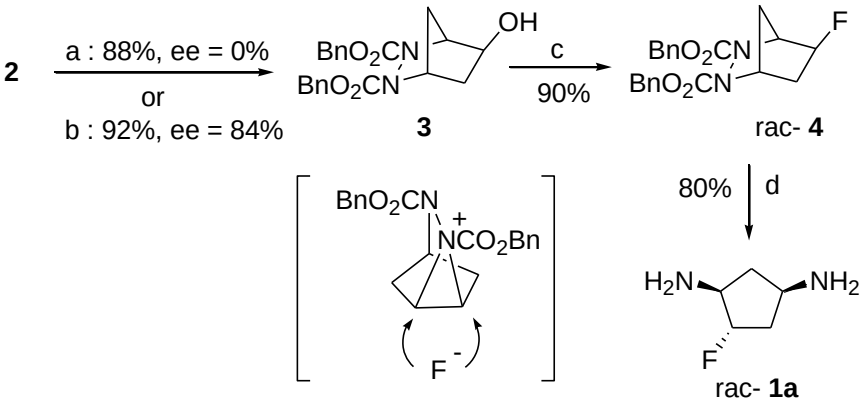


FIGURE 1. General strategy for the synthesis of fluorinated diaminocyclopentanes from bicyclic hydrazine **2**

Although a direct electrophilic fluorination of the strained double bond of compound **2** can be envisaged, all the reaction conditions previously reported on norbornene or structurally related compounds failed to deliver any fluorinated adducts with compound **2**.[6] We then decided to introduce the fluorine atom starting from the corresponding alcohol (Scheme 1).

SCHEME 1. Synthesis of Compound *rac*-1a [a]



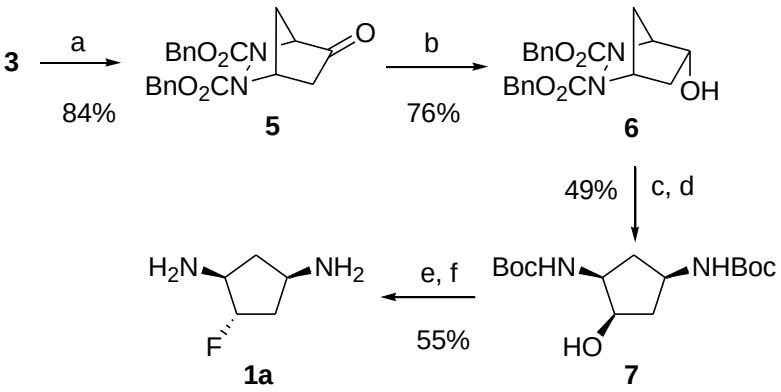
[a] Reagents and conditions: (a) BH_3.THF, THF, 0 °C, then H_2O_2, NaOH, 0 °C to r.t. (b) Catecholborane, 1% $[Rh(COD)Cl]_2$, 2% (*R*,*R*)-bdpp, DME, -50 °C, then H_2O_2, NaOH, 0 °C to rt. (c) DAST, CH_2Cl_2, 0 °C. (d) H_2, Pd/C, MeOH.

Alcohol **3** was prepared using either racemic or asymmetric hydroboration.[7] Reaction with *N*,*N*-diethylaminosulfur trifluoride (DAST) led to the corresponding fluorinated bicycle **4** as a

single diastereomer. The full retention of relative configuration can be explained by the formation of a transient aziridinium.[8,9] The formation of this *meso* intermediate was confirmed by the obtention of racemic material **4** from enantioenriched (er = 92:8) alcohol **3**. Racemic diamine **1a** was then obtained in 80% yield after reductive hydrogenolysis.

As the fluorination of bicyclic alcohol **3** is a racemizing process, we envisaged the preparation of non-racemic **1a** from the all-*cis* protected diamino-alcohol **7** (Scheme 2). The *cis* relationship between the leaving group and the neighbouring carbon-nitrogen bound precludes any anchimeric participation, enabling the formation of enantioenriched **1a** with full inversion of configuration. Non-racemic compound **7** could be prepared from **3** by oxidation and reduction, delivering enantioenriched compound **6**, which was hydrogenolyzed and protected by *tert*-butyl carbamate groups.

SCHEME 2. Synthesis of Enantioenriched 1a [a]

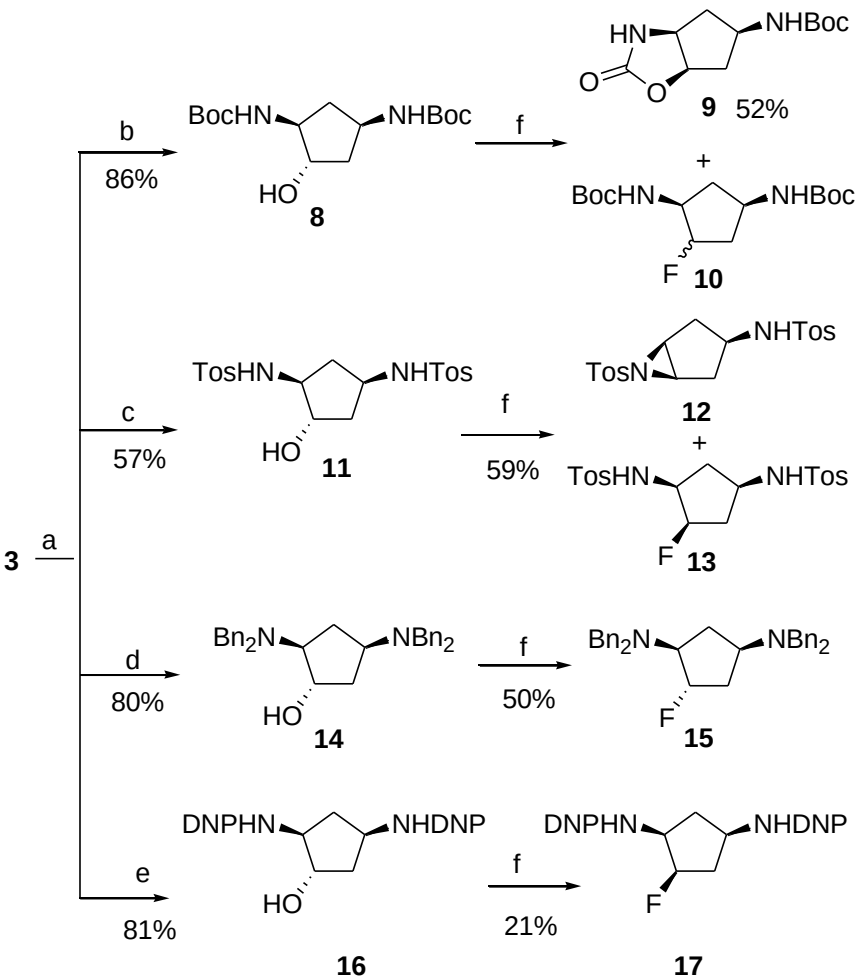


[a] Reagents and conditions: (a) $(COCl)_2$, Et_3N, DMSO. (b) BH_3.THF, THF. (c) H_2, Pd/C, MeOH. (d) Boc_2O, K_2CO_3, THF-H_2O. (e) DAST, CH_2Cl_2, 0 °C. (f) HCl, AcOEt.

The preparation of *cis*-compound **1b** from alcohol **3** was then investigated. Obtention of a 1,2 *syn* relative configuration requires the fluorination with inversion of configuration. As this stereochemical outcome is not possible, working on the bicyclic structure, hydrazine **3** was

first reductively cleaved and the two amines were protected by several protective groups (Scheme 3).

SCHEME 3. Protective Group Influence on the Fluorination Step [a]

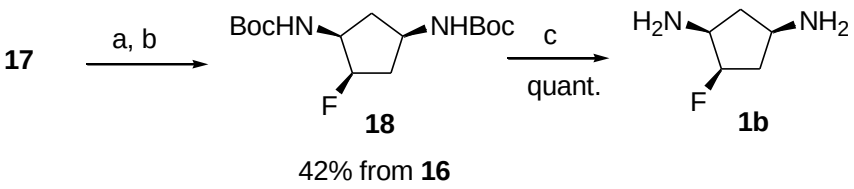


[a] Reagents and conditions. (a) H_2, Pd/C, MeOH or H_2, PtO_2, AcOH (b) Boc_2O, K_2CO_3, THF-H_2O (c) TsCl, CH_2Cl_2-NaOH (1M). (d) BnBr, H_2O-Acetone, K_2CO_3 (e) 2,4-dinitro-1-fluorobenzene, Et_3N, THF (f) DAST, CH_2Cl_2.

The fluorination of the protected diaminocyclopentanols having a 1,2-aminoalcohol *trans* configuration without participation of the neighbouring groups proved to be difficult. Thus, treatment of compound **8** with DAST led to the oxazolidinone **9** in 52% isolated yield, accompanied with a diastereomeric mixture of **10** as side products. Tosyl protective groups were introduced in order to avoid the participation of the carbonyl groups of the carbamates.

However, the fluorination proved also to be troublesome, leading to a mixture of products with *meso* aziridine **12** as a major component. The use of *N,N'*-tetrabenzyl **14** led to a single fluorinated isomer, albeit with the *trans* configuration, again *via* a transient *meso* aziridinium intermediate. Finally, protection of the diamino alcohol **3** with 2,4-dinitrophenyl (DNP)[10] enabled the fluorination of **16** with full inversion of configuration in 21% yield. This modest chemical yield can be explained by the low solubility of DNP-protected compounds, leading to purification problems. As this transformation doesn't involve any *meso* intermediate, it could also be conducted from enantioenriched material, leading to enantioenriched compound **17**. Compound **1b** was finally obtained after a sequence of deprotection-protection for purification, followed by removal of the Boc groups under acidic conditions (Scheme 4).

SCHEME 4. Synthesis of Compound 1b [a]

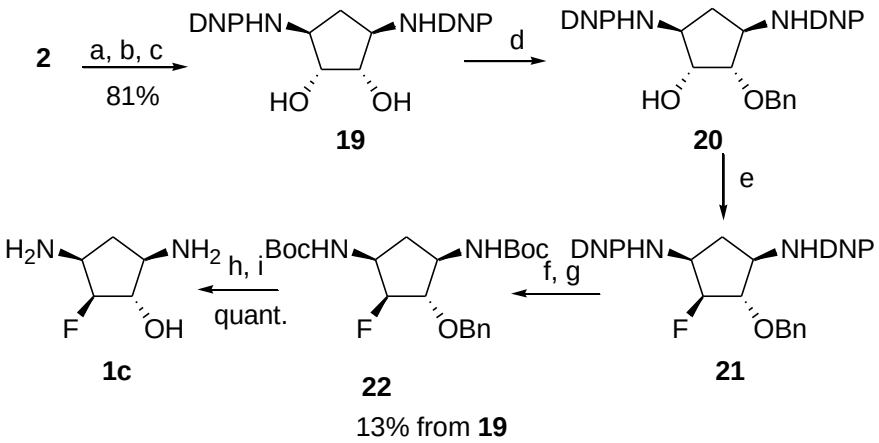


[a] Reagents and conditions: (a) Amberlite 400 IRA resin (OH^- form), acetone-H_2O. (b) Boc_2O, THF-$NaOH_{aq}$. (c) HCl, AcOEt.

A similar protective group strategy was used for the preparation of compound **1c** (Scheme 5). Dihydroxylation of compound **2**, followed by reductive cleavage and protection, led to the diol **19**. Monoprotection of **19** led to compound **20**, which could be treated by DAST to deliver the protected fluorinated tetrasubstituted cyclopentane as a single diastereomer. The two dinitrophenyl groups of compound **21** were removed under basic conditions, and the amines were reprotected by *tert*-butyl carbamates. 1,2,3,4-tetrasubstituted cyclopentane **22** was purified at this stage and isolated in 13% overall yield from **19**. Compound **1c** was then

obtained as its hydrochloride form after hydrogenolysis and acidification in a quantitative yield.

SCHEME 5. Synthesis of Compound 1c [a]

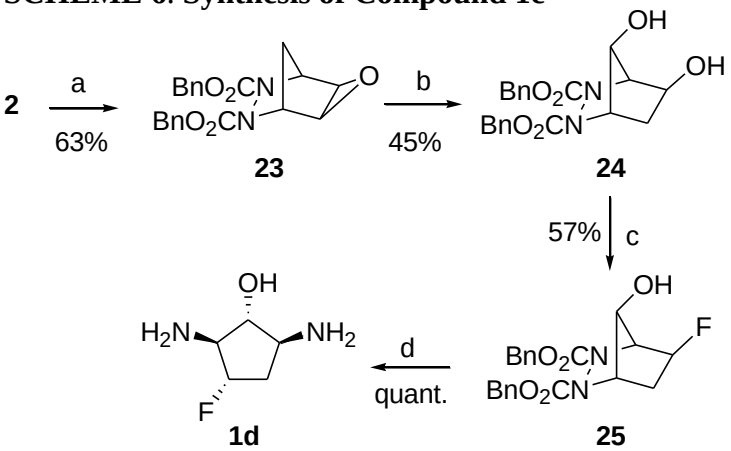


[a] Reagents and conditions: (a) OsO_4, NMO, THF-H_2O (b) H_2, PtO_2, AcOH. (c) 2,4-dinitro-1-fluorobenzene, $NaHCO_3$, H_2O. (d) BnBr, KHMDS, THF. (e) DAST, THF, 0 °C. (f) Amberlite 400 IRA resin (OH^- form), acetone-H_2O. (g) Boc_2O, THF-$NaOH_{aq}$. (h) H_2, Pd/C, MeOH. (i) HCl, AcOEt.

The synthesis of 1,2,4,5-tetrasubstituted cyclopentane **1d** was then envisaged (Scheme 6). Compound **24** was prepared in two steps from **2** in 28% yield. The treatment of **24** with DAST delivered compound **25** as a single product in a diastereoselective manner. Compound **1d** was then obtained quantitatively after hydrogenolysis.

The chemo- and diasteroselectivity for the fluorination of diol **24**[9] is noteworthy. This selective process can be explained as follows (Scheme 7). Both hydroxyl groups can probably react with the excess of DAST, leading to a bis-activated intermediate **A**. The presence of the hydroxymethylene bridge restricts the conformational freedom of the carbamates, enabling the nitrogen lone pairs of the hydrazine to be either pseudo equatorial or pseudo *endo* axial.

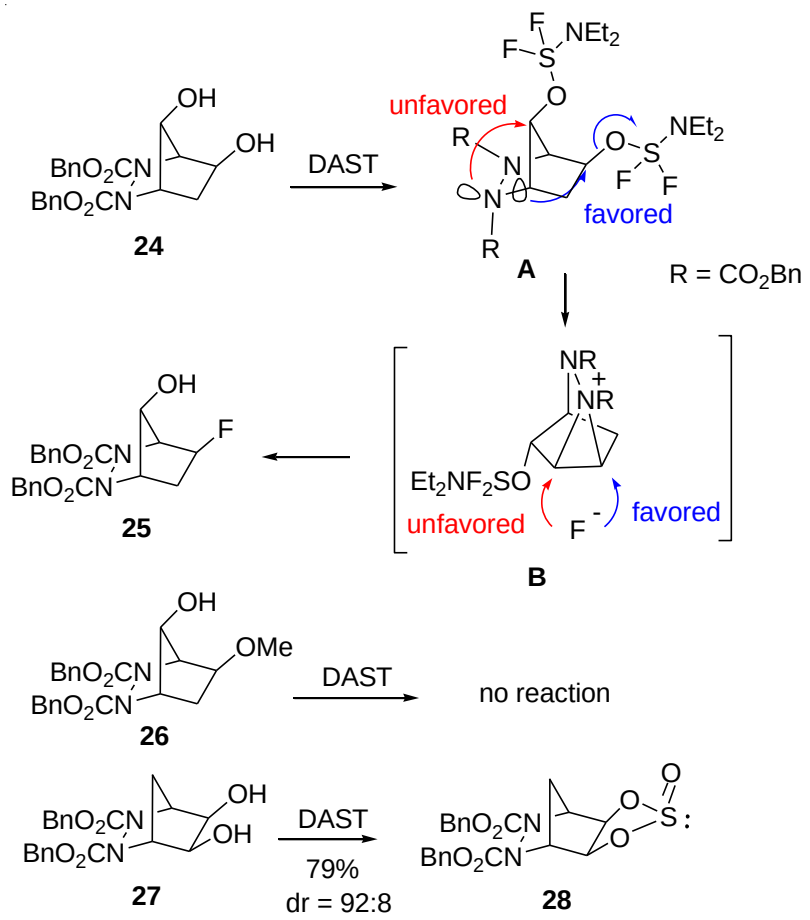
SCHEME 6. Synthesis of Compound 1c [a]



[a] Reagents and conditions: (a) m-CPBA, CH_2Cl_2, 40 °C. (b) H_2SO_4, CF_3CH_2OH. (c) DAST, THF, 0 °C to r.t. (d) H_2, Pd/C, MeOH.

As a consequence, stereoelectronic effects will favor the departure of the leaving group located on the ethylene bridge, leading to an aziridinium intermediate **B**. A direct attack of the hydroxymethylene group by a fluoride is probably inhibited by the presence of one of the carbamate groups. This effect was confirmed by the absence of reactivity of compound **26** under similar conditions. The regioselective opening of this intermediate is the result of a steric hindrance caused by the second activated hydroxyl group. Interestingly, this selective fluorination couldn't be observed starting from 1,2-diol **27**,[12] as the competitive highly diastereoselective formation of a cyclic sulfite **28** was observed.

SCHEME 7. Fluorination of Bicyclic Hydrazinodiols



In conclusion, we have shown that several fluorinated 1,3-diaminocyclopentanes can be prepared in a diastereoselective manner from a single bicyclic hydrazine precursor, in 3 to 9 steps. The use of DAST as a fluorinating agent enabled the selective formation of the carbon fluorine bond from an alcohol, with inversion or retention of configuration, and in some cases skeleton rearrangement. The final fluorinated diamines have been shown to be interesting topological probes to study RNA structures, but can also serve as novel building block for the design of bio-active compounds.

Experimental section

Compounds **2**, **3**, **5** have been previously described.[7] Compounds **4**, **6**, **7**, **1a, 1b, 1c, 1d** have been previously described.[5] Compound **8** has been previously described.[11] Compounds **23**, **24, 26** have been previously described.[9] Compound **27** has been previously described.[12]

(2-Oxo-hexahydrocyclopentaoxazol-5-yl)carbamic acid *tert*-butyl ester 9

DAST (82 µL, 0.62 mmol) was added to a cooled (-78 °C) suspension of compound **8** (100 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (3 mL). After stirring for 2 h, the reaction mixture was allowed to reach 0 °C, and quenched with an aqueous saturated solution of $NaHCO_3$ (10 mL). CH_2Cl_2 (10 mL) was added, and the organic layer was separated, washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/MeOH 97:3) gave compound **9** (40 mg, 0.17 mmol, 52%) as a white powder: mp 186 °C. ^{1}H NMR (300 MHz, 300 K, CD_3OD) *δ:* 6.54 (br. s, 1H), 5.06 (ddd, *J* = 7.9, 6.3, 3.5 Hz, 1H), 4.23 (td, *J* = 6.3, 3.5 Hz, 1H), 3.92 (sext., *J* = 6.3 Hz, 1H), 2.26 (dt, *J* = 13.8, 6.3 Hz, 1H), 2.15 (dt, *J* = 13.4, 6.3 Hz, 1H), 2.08-1.97 (m, 1H), 1.83 (dt, *J* = 13.8, 6.3 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, 300 K, CD_3OD) *δ:* 161.4, 158.0, 82.7, 80.3, 57.1, 51.6, 40.8, 39.9, 28.7. ESI HRMS: [MNa^+] calculated for $C_{11}H_{18}N_2O_4Na$ 265.1164, found 265.1164.

2,4-Ditosylaminocyclopentanol 11

A solution of **3** (2.5 g, 6.54 mmol) in MeOH (50 mL) was stirred under hydrogen atmosphere in the presence of Pd/C (1 g) for 3 days. The reaction mixture was then filtered through a celite pad, washed with a 1:1 MeOH/CH_2Cl_2 mixture, and evaporated *in vacuo* to give the deprotected diaminoalcohol (610 mg, 5.26 mmol). The diaminoalcohol (410 mg, 3.53

mmol) was dissolved in a 1:1 mixture of CH_2Cl_2/1M NaOH (15 mL). Tosylchloride (1.35 g, 7.1 mmol) was added and the reaction mixture was stirred for 15 h. The aqueous phase was separated and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography (cyclohexane-AcOEt, 4:6) gave compound **11** (850 mg, 57%) as a white powder: mp 78-80 °C. ^{1}H NMR (300 MHz, 300 K, $CDCl_3$) *δ:* 7.70 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.00 (d, *J* = 6.5 Hz, 1H), 5.77 (d, *J* = 6.8 Hz, 1H), 4.15 (q, *J* = 6.5 Hz, 1H), 3.61 (sext., *J* = 6.8 Hz, 1H), 3.21 (quint., *J* = 6.5 Hz, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 2.07 (dt, *J* = 14.3, 6.8 Hz, 1H), 1.79 (dt, *J* = 14.1, 6.8 Hz, 1H), 1.68 (dt, *J* = 14.1, 6.8 Hz, 1H), 1.36 (dt, *J* = 14.3, 6.8 Hz, 1H). ^{13}C NMR (75 MHz, 300 K, $CDCl_3$) *δ:* 143.8, 143.6, 136.9, 136.4, 129.9, 129.8, 127.2, 127.1, 60.2, 50.2, 39.0, 37.8, 21.5. ESI MS: [MNa^+] 447, [MK^+] 463.

Compounds 12 and 13

To a cooled (0 °C) solution of **11** (150 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (5 mL) under argon atmosphere was added DAST (95 µL, 0.71 mmol). The mixture was stirred at room temperature for 3 h, and quenched with an aqueous saturated solution of $NaHCO_3$ (10 mL). The organic layers were separated, washed with brine (3 × 10 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography (cyclohexane-AcOEt, 7:3) gave an inseparable mixture of compounds **12** and **13** (75:25, 85 mg, 59% yield of the mixture). Each compound was characterized from the mixture, but not isolated. **4-Methyl-*N*-[6-(toluene-4-sulfonyl)-6-azabicyclo[3.1.0]hex-3-yl]benzenesulfonamide 12:** ^{1}H NMR (300 MHz, 300 K, $CDCl_3$) *δ*: 7.81 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 3.85 (dt, *J* = 10.8, 7.4 Hz, 1H), 3.35 (s, 2H), 2.50 (s, 3H), 2.43 (s, 3H), 1.95 (dd, *J* = 14.9, 7.4 Hz, 2H), 1.77 (m, 2H). ^{13}C

NMR (75 MHz, 300 K, $CDCl_3$) δ: 144.9, 143.4, 138.2, 135.0, 129.9, 129.8, 127.9, 126.9, 50.9, 46.1, 35.3, 21.7, 21.6. ESI MS: [MNa^+] 429. **4-Fluorocyclopentane-1,3-ditosylamine 13:** ^{1}H NMR (300 MHz, 300 K, $CDCl_3$) δ: 7.71 (dd, J = 8.1, 5.0 Hz, 4H), 7.29 (d, J = 6.4 Hz, 4H), 5.14 (d, J = 9.6 Hz, 1H), 4.96 (d, J = 9.2 Hz, 1H), 4.51 (dt, J = 54.2, 3.6 Hz, 1H), 3.68 (td, J = 8.5, 3.6 Hz, 1H), 3.59-3.38 (dm, J = 27 Hz, 1H), 2.43 (s, 6H), 2.17 (dt, J = 13.9, 8.5 Hz, 1H), 1.78-1.72 (m, 1H), 1.66 (m, 2H), 1.38 (m, 1H). ^{13}C NMR (75 MHz, 300 K, $CDCl_3$) δ: 143.7, 143.6, 137.5, 137.4, 129.9, 129.8, 127.2, 127.0, 94.6 (d, J = 177 Hz), 55.6 (d, J = 19 Hz), 49.7, 38.1 (d, J = 20 Hz), 36.8, 21.7, 21.6. ^{19}F NMR (282MHz, 300 K, $CDCl_3$) δ: -189.4. ESI MS: [MNa^+] 449, [MK^+] 465.

2,4-Bis-dibenzylaminocyclopentanol 14

To a suspension of 2,4-diaminocyclopentanol (420 mg, 3.6 mmol) in a water-acetone mixture (1:3, 36 mL) were added potassium carbonate (4.48 g, 32.4 mmol) and benzyl bromide (1.88 mL, 15.8 mmol). The reaction mixture was stirred at room temperature for 42 h and then acetone was evaporated *in vacuo*. Water was added (15 mL) and the product was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash chromatography (cyclohexane-AcOEt, 85:15 then 80:20) gave compound **14** (1.36 g, 80%) as a pale yellow solid: mp 101-102 °C. ^{1}H NMR (400 MHz, 300 K, $CDCl_3$) δ: 7.45 (m, 16H), 7.33 (m, 4H), 4.24 (q, J = 7.5 Hz, 1H), 3.91 (d, J = 13.7 Hz, 1H), 3.71 (s, 4H), 3.62 (d, J = 13.7 Hz, 1H), 3.44 (m, 1H), 2.98 (td, J = 11.7, 7.5 Hz, 1H), 2.1 (m, 2H), 1.75 (m, 2H). ^{13}C NMR (100 MHz, 300 K, $CDCl_3$) δ: 172.6, 139.9, 128.5, 128.3, 128.2, 127.0, 126.8, 72.1, 67.1, 55.8, 55.0, 54.7, 34.2, 25.4. HRMS calculated for $C_{33}H_{37}N_2O$ 477.2906, found 477.2905.

1,3-Bis-dibenzylamino-4-fluorocyclopentanol 15

A solution of **14** (194 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 °C. After addition of DAST (110 µL, 0.82 mmol), the reaction mixture was stirred at room temperature for 1 h. Water was added and the solution was extracted with CH_2Cl_2. The combined organic layers were washed with an aqueous saturated solution of NH_4Cl, dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography (cyclohexane-AcOEt, 99:1) gave compound **15** (98 mg, 50%) as a white powder: mp 123-125 °C. ^{1}H NMR (300 MHz, 300 K, $CDCl_3$) δ: 7.31-7.48 (m, 20H), 5.20 (br. d, J = 54 Hz, 1H), 3.64-3.80 (m, 8H), 3.35-3.46 (m, 2H), 2.09-2.21 (m, 2H), 1.87-2.06 (m, 1H), 1.68-1.79 (m, 1H). ^{13}C NMR (75 MHz, 300 K, $CDCl_3$) δ: 139.7 (d, J = 23 Hz), 128.7, 128.6, 128.3, 126.3, 96.4, 65.7 (d, J = 23 Hz), 57.8, 55.3 (d, J = 3 Hz), 35.7 (d, J = 22 Hz), 30.3 (d, J = 5 Hz). ^{19}F NMR (282 MHz, 300 K, $CDCl_3$) δ: -168.8 (ddt, J = 54, 30, 24 Hz). ESI HRMS: [MNa^+] calculated for $C_{33}H_{35}FN_2Na$ 501.2682, found 501.2681.

2,4-Bis-(2,4-dinitrophenylamino)cyclopentanol 16

2,4-diaminocyclopentanol, prepared from enantioenriched **3** by Pd/C catalyzed hydrogenolysis (185 mg, 1.6 mmol, 83% ee) was dissolved in anhydrous THF (5 mL) containing Et_3N (500 µL, 3.5 mmol). 2,4-dinitro-1-fluorobenzene (440 µL, 3.5 mmol) was added. The bright yellow solution was stirred for 5h at room temperature, and the solvent was evaporated *in vacuo*. The crude mixture was stirred in MeOH (5 mL) for 15 h, and the resulting solid was filtered, washed with CH_2Cl_2, and dried *in vacuo* to give **16** (580 mg, 1.3 mmol, 81%) as an amorphous yellow solid: ^{1}H NMR (300 MHz, 300 K, DMSO-d_6) δ: 8.85 (d, J = 2.7 Hz, 2H), 8.63 (br. d, J = 8.2 Hz, 1H), 8.61 (br. d, J = 8.2 Hz, 1H), 8.31 (dd, J = 9.6, 2.7 Hz, 1H), 8.30 (dd, J = 9.6, 2.7 Hz, 1H), 7.39 (d, J = 9.6 Hz, 1H), 7.26 (d, J = 9.6 Hz, 1H), 5.49 (s, 1H), 4.43 (sext., J = 7.8 Hz, 1H), 4.31-4.22 (m, 1H), 4.12-3.98 (m, 1H), 2.82 (dt, J = 13.4, 7.8 Hz, 1H), 2.21-2.02 (m, 2H), 1.95 (dt, J = 13.4, 7.8 Hz, 1H). ^{13}C NMR (75 MHz, 300

K, DMSO-d_6) δ: 147.9, 147.3, 135.1, 135.0, 130.1, 130.0, 129.9, 123.5, 116.0, 115.6, 74.6, 60.4, 50.2, 38.6, 36.2. HRMS calculated for $C_{17}H_{16}N_6O_9Na$ 471.0871, found 471.0875. $[\alpha]_D^{22}$: +19.8 (c = 0.17, $CHCl_3$).

4-Fluorocyclopentane-1,3-Bis-(2,4-dinitrophenylamine) 17

DAST (55 µL, 0.43 mmol) was added to a cooled (0 °C) suspension of compound **16** (96 mg, 0.21 mmol) in anhydrous CH_2Cl_2 (5 mL) under argon atmosphere. The reaction mixture was stirred at room atmosphere for 45 min and quenched with an aqueous saturated solution of $NaHCO_3$. The aqueous phase was separated and extracted twice with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/AcOEt 90:10) gave compound **17** (20 mg, 0.05 mmol, 21%) as an amorphous yellow solid: ^{1}H NMR (300 MHz, 300 K, DMSO-d_6) δ: 8.86 (d, J = 2.7 Hz, 1H), 8.84 (d, J = 2.7 Hz, 1H), 8.75 (br. d, J = 8.2 Hz, 1H), 8.67 (br. d, J = 7.5 Hz, 1H), 8.33 (dd, J = 9.6, 2.7 Hz, 1H), 8.30 (dd, J = 9.6, 2.7 Hz, 1H), 7.41 (d, J = 9.6 Hz, 1H), 7.27 (d, J = 9.6 Hz, 1H), 5.34 (dt, J = 57.0, 3.7 Hz, 1H), 4.59-4.36 (m, 2H), 2.95 (dt, J = 12.8, 7.7 Hz, 1H), 2.67 (dddd, J = 41.0, 15.6, 8.4, 4.2 Hz 1H), 2.50 (ddd, J = 26.4, 15.6, 3.7 Hz, 1H), 2.00-1.91 (ddd, J = 12.8, 10.4, 7.7 Hz, 1H). ^{13}C NMR (75 MHz, 300 K, DMSO-d_6) δ: 147.5, 147.1, 135.5, 135.2, 130.2, 130.1, 130.0, 123.4, 115.8, 115.5, 94.3, 55.1, 50.2, 37.4, 35.8. ^{19}F NMR (282 MHz, 300 K, DMSO-d_6) δ: -189.0 (ddt, J = 57.0, 41.0, 26.4 Hz). HRMS calculated for $C_{17}H_{15}FN_6O_8$ 450.0935, found 450.0935.

(3-*tert*-Butoxycarbonylamino-4-fluorocyclopentyl)carbamic acid *tert*-butyl ester 18

The crude product **17** (0.9 mmol) was dissolved in an acetone-water mixture (50:15, 65 mL). Amberlite 400 IRA resin (OH^- form, 6 g) was added, and the reaction mixture was stirred at room temperature for 2 days, filtered through a celite pad, and washed with a THF-

MeOH-H_2O (1:1:1) solution. The organic solvents were removed *in vacuo*, and the resulting aqueous solution was basified to pH 10 using NaOH (1M). THF (15 mL) and Boc_2O (590 mg, 2.7 mmol) were added. After stirring for 20 h, THF was evaporated, and AcOEt (25 mL) and H_2O (25 mL) were added. The aqueous phase was separated and extracted with AcOEt (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/MeOH 98:2) gave compound **18** (120 mg, 0.38 mmol, 42% yield from **16**) as an amorphous white solid: ^{1}H NMR (300 MHz, 300 K, $CDCl_3$) δ: 4.89 (br. d, J = 55.3 Hz, 1H), 4.81 (br. s, 1H), 4.67 (br. s, 1H), 4.10-3.78 (m, 2H), 2.52 (dt, J = 15.5, 7.7 Hz, 1H), 2.28 (dddd, J = 42.0, 15.7, 9.5, 4.1 Hz, 1H), 1.81 (ddd, J = 26.8, 15.7, 3.4 Hz, 1H), 1.56-1.30 (m, 19H). ^{13}C NMR (75 MHz, 300 K, DMSO-d_6) δ: 155.2, 155.1, 94.7 (d, J = 178 Hz), 79.8, 79.5, 53.8 (d, J = 17 Hz), 47.7, 38.9 (d, J = 20 Hz), 37.1, 28.4. ^{19}F NMR (282 MHz, 300 K, $CDCl_3$) δ: -190 (m). ESI HRMS: [MNa^+] calculated for $C_{15}H_{27}FN_2O_4Na$ 341.1853, found 341.1855. $[\alpha]_D^{22}$: -5.1 (c = 1, $CHCl_3$).

Synthesis of *rac*-3,5-Diamino-2-fluorocyclopentanol 1c:

Compound **2** (5 g, 13.7 mmol) was dissolved in THF-H_2O (145 mL:15 mL). NMO (2 g, 16.8 mmol) and potassium osmate (40 mg, 0.11 mmol) were added and the reaction mixture was stirred at room temperature for 18 h. HCl (6N, 200 mL) and $NaHSO_3$ (15% in water, 100 mL) were added and the mixture was stirred for 2 h. With AcOEt (200 mL) added, the organic phase was separated, and the aqueous layer was extracted with AcOEt (3 × 200 mL). The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (cyclohexane-AcOEt 60:40) gave compound **27** as a colourless oil (5 g, 12.6 mmol, 90% yield). Compound **27** (5 g) was then stirred in acetic acid (80 mL) under hydrogen atmosphere in the presence of PtO_2 (750 mg, 3 mmol) for 3 days. After filtration

through a celite pad and concentration *in vacuo*, the crude product was purified on a DOWEX resin (50WX8-400) using a 1M aqueous solution of ammonia as eluting phase, to give colourless oil in a quantitative yield (1.65 g). ^{1}H NMR (300 MHz, 323 K, CD_3OD) δ: 3.66 (m, 2H), 3.09 (ddm, J = 8.8, 8.0 Hz, 2H), 2.36 (dt, J = 13.5, 8.0 Hz, 1H), 1.06 (dt, J = 13.5, 8.8 Hz, 1H). ^{13}C NMR (75 MHz, 323 K, CD_3OD) δ: 79.8, 57.0, 39.0. ESI MS: [MH^+] 133, [MNa^+] 155. This diaminodiol (1.3 g, 9.8 mmol) was dissolved in an aqueous saturated solution of $NaHCO_3$ (75 mL) and 2,4-dinitrofluorobenzene (2.5 mL, 19.9 mmol) was added. The bright yellow solution was stirred for 18 h. The precipitate was filtered, stirred in CH_2Cl_2 for 3 h, and dried under vacuum to give compound **19** (4.1 g, 90%) as a yellow amorphous solid. **3,5-Bis-(2,6-dinitrophenylamino)cyclopentane-1,2-diol 19** ^{1}H NMR (300 MHz, 323 K, DMSO-d_6) δ: 8.87 (d, J = 2.6 Hz, 2H), 8.66 (br. s, 2H), 8.31 (dd, J = 9.6, 2.6 Hz, 2H), 7.39 (d, J = 9.6 Hz, 2H), 6.22 (br. s, 2H), 4.20-4.06 (m, 2H), 3.97 (d, J = 3.8 Hz, 2H), 2.77 (dt, J = 13.0, 8.2 Hz, 1H), 1.89 (dt, J = 13.0, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, 323 K, DMSO-d_6) δ: 147.9, 135.1, 130.0, 129.9, 123.5, 116.0, 75.3, 57.1, 32.7. ESI HRMS: [MNa^+] calculated for $C_{17}H_{16}N_6O_{10}Na$ 487.0826, found 487.0824.

To a cooled (0 °C) solution of compound **19** (1.4 g, 3 mmol) and benzylbromide (1.45 mL, 12 mmol) in anhydrous THF (45 mL) was slowly (2 mL.h^{-1}) added KHMDS (0.5M in toluene, 7.3 mL, 3.5 mmol). The reaction mixture was then stirred at room temperature for 20 h and quenched with an aqueous saturated solution of NH_4Cl. Aqueous layer was extracted with AcOEt (4 × 100 mL), and the combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was stirred in CH_2Cl_2 for 4 h, and dried under vacuum to give a 1:1 mixture of compounds **19** and **20**. A small portion was purified by flash chromatography (Toluene-THF 80:20, then 70:30, then THF) for characterization of compound **20. 2-Benzyloxy-3,5-bis-(2,6-dinitrophenylamino)cyclopentanol 20** ^{1}H NMR (300 MHz, 293 K, DMSO-d_6) δ: 8.88 (d, J = 2.6 Hz, 1H), 8.86 (d, J = 2.6 Hz, 1H), 8.67 (d, J

= 8.2 Hz, 1H), 8.60 (d, *J* = 8.2 Hz, 1H), 8.35 (dd, *J* = 9.6, 2.6 Hz, 1H), 8.24 (dd, *J* = 9.6, 2.6 Hz, 1H), 7.44-7.20 (m, 7H), 5.57 (d, *J* = 5.5 Hz, 1H), 4.74 (d, *J* = 12.3 Hz, 1H), 4.50 (d, *J* = 12.3 Hz, 1H), 4.38 (q, *J* = 8.2 Hz, 1H), 4.19 (q, *J* = 5.5 Hz, 1H), 4.11 (dd, *J* = 8.2, 5.5 Hz), 4.02 (t, *J* = 5.5 Hz, 1H), 2.81 (dt, *J* = 13.0, 8.2 Hz, 1H), 1.91 (dt, *J* = 13.0, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, 293 K, DMSO-d_6) δ: 147.8, 147.6, 138.3, 135.2, 135.1, 130.1, 130.0, 129.9, 129.8, 128.1, 127.4, 127.3, 123.5, 116.0, 115.9, 82.5, 73.3, 71.3, 57.5, 55.4, 32.4.

To a cooled (0 °C) suspension of compounds **19** and **20** (1:1, 200 mg) in anhydrous THF (8 mL) under argon atmosphere was added DAST (190 μL, 1.44 mmol). The reaction mixture was stirred at room temperature for 3 h and quenched by an aqueous saturated solution of $NaHCO_3$. The aqueous layer was extracted with AcOEt, and the combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was not purified at this stage, and dissolved in acetone-water (36:4, 40 mL). Amberlite 400 IRA resin (OH^- form, 3 g) was added, and the mixture was stirred at room temperature for 2 days, filtered through a celite pad, and washed with a THF-MeOH-H_2O (1:1:1) solution. The organic solvents were removed *in vacuo*, and the resulting aqueous solution was basified using NaOH (1M, 20 mL). THF (20 mL) and Boc_2O (630 mg, 2.88 mmol) were added. After 15 h stirring, THF was evaporated, and AcOEt (30 mL) and H_2O (10 mL) were added. The aqueous layer was extracted with AcOEt (3 × 20 mL), the combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. Purification by flash chromatography (cyclohexane-AcOEt 70:30 to 50:50) gave **22** as an amorphous solid (17 mg, 13% yield from **19**). **(3-Benzyloxy-4-*tert*-butoxycarbonylamino-2-fluorocyclopentyl)carbamic acid *tert*-butyl ester 22** ^{1}H NMR (300 MHz, 333 K, DMSO-d_6) δ: 7.46-7.18 (m, 5H), 6.67 (s, 1H), 6.46 (s, 1H), 4.77 (ddd, *J* = 52, 4.9, 2.5 Hz, 1H), 4.62 (s, 2H), 3.99-3.69 (m, 3H), 2.29-2.15 (dt, *J* = 11.1, 7.5 Hz, 1H) 1.64 (q, *J* = 11.1 Hz, 1H), 1.42 (s, 9H), 1.41 (s, 9H). ^{13}C NMR (75 MHz, 293 K, DMSO-d_6) δ: 155.0, 154.9, 137.9, 128.1, 127.4, 127.4, 94.0 (d, *J* = 183 Hz), 86.4 (d, *J* = 25 Hz), 77.9, 77.8,

70.6, 52.7, 49.8 (d, J = 19 Hz), 32.8. ^{19}F NMR (282 MHz, 293 K, CD_3OD) δ: - 199.3 (dt, J = 52, 24 Hz). ESI HRMS: [MNa^+] calculated for $C_{22}H_{33}FN_2O_5Na$ 447.2271, found 447.2274.

Compound **22** (35 mg, 0.08 mmol) in MeOH (4 mL) was stirred under hydrogen atmosphere in the presence of Pd/C (9 mg) for 50 h. The reaction mixture was filtered through a celite pad, and the solvent was concentrated *in vacuo*. The crude product (28 mg, 0.08 mmol) was dissolved in AcOEt (10 mL) and HCl(g) was bubbled for 45 min. Compound **1c** (17 mg, 0.1 mmol) was isolated as its hydrochloride salt in a quantitative yield. ^{1}H NMR (300 MHz, 293 K, CD_3OD) δ: 5.03 (ddd, J = 52.1, 5.5, 2.1 Hz, 1H), 4.31 (ddd, J = 23.3, 6.3, 2.1 Hz, 1H), 3.90 (dddd, J = 23.3, 11.7, 7.3, 5.5 Hz, 1H), 3.47 (ddd, J = 11.7, 7.3, 6.3 Hz, 1H), 2.66 (dt, J = 11.7, 7.3 Hz, 1H), 2.00 (q, J = 11.7 Hz, 1H). ^{13}C NMR (75 MHz, 293 K, CD_3OD) δ: 96.9 (d, J = 185 Hz), 78.8 (d, J = 27 Hz), 55.2 (d, J = 6 Hz), 49.7 (d, J = 18 Hz), 31.6. ^{19}F NMR (282 MHz, 293 K, CD_3OD) δ: -199.1 (dt, J = 52.1, 23.3 Hz). ESI HRMS: [MH^+] calculated for $C_5H_{12}FN_2O$ 135.0934, found 135.0923.

Synthesis of *rac*-2,5-Diamino-3-fluorocyclopentanol 1d:

To a dry THF (10 mL) solution of diol **24**, (375 mg, 0.94 mmol), prepared according to ref 9, cooled at 0 °C under argon atmosphere, was added DAST (190 μL, 1.95 mmol). The reaction mixture was stirred at room temperature for 15 h, and hydrolyzed by an aqueous $NaHCO_3$ solution (5 mL). The mixture was extracted with AcOEt (3 × 10 mL), and the combined organic layers were washed with brine and dried ($MgSO_4$), then concentrated *in vacuo*. Purification by flash chromatography (cyclohexane-AcOEt 80:20) gave compound **25** as colourless oil (215 mg, 57% yield). **5-Fluoro-7-hydroxy-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylic acid dibenzyl ester 25** ^{1}H NMR (300 MHz, 323 K, DMSO-d_6) δ: 7.53-7.18 (m, 10H), 5.30 (br.s, 1H), 5.17 (s, 2H), 5.15 (s, 2H), 4.80 (dm, J = 53 Hz, 1H), 4.33-4.29 (m, 2H), 4.10 (s, 1H), 2.29 (dm, J = 4.2 Hz, 1H), 2.21 (m, 1H). ^{13}C NMR (75 MHz, 323 K,

DMSO-d_6) δ: 156.6; 155.7, 135.6, 128.1, 127.8, 127.3, 89.8 (d, J = 193 Hz), 73.6, 67.2, 61.6, 34.6 (d, J = 19 Hz). ^{19}F NMR (282 MHz, 323 K, DMSO-d_6) δ: - 174.0 (m). ESI HRMS: [MNa$^+$] calculated for $C_{21}H_{21}FN_2O_5Na$ 423.1327, found 423.1327. [MK$^+$] calculated for $C_{21}H_{21}FN_2O_5K$ 439.1066, found 439.1057.

Compound **25** (40 mg, 0.1 mmol) was stirred in methanol (3 mL) under hydrogen atmosphere in the presence of Pd/C (21 mg, 0.02 mmol) for 15 h. The mixture was filtered through a celite pad, and the solvent was concentrated *in vacuo*. The crude product was dissolved in AcOEt-MeOH (1:1, 10 mL) and HCl(g) was bubbled for 1 min. Compound **1d** (20 mg, 0.1 mmol) was isolated as its hydrochloride salt in a quantitative yield. ^{1}H NMR (300 MHz, 293 K, CD_3OD) δ: 5.17 (dddd, J = 52.7, 8.2, 5.2, 3.0 Hz, 1H), 4.17 (t, J = 9.4 Hz, 1H), 3.67 (q, J = 9.4 Hz, 1H), 3.62 (ddd, J = 24.2, 9.4, 5.2 Hz, 1H), 2.39 (m, 2H). ^{13}C NMR δ: (75 MHz, 293 K, CD_3OD): 91.3 (d, J = 185 Hz), 75.7 (d, J = 5 Hz), 62.4 (d, J = 25 Hz), 54.2, 33.1 (d, J = 24 Hz). ^{19}F NMR (282 MHz, 293 K, CD_3OD) δ: -176.7 (dq, J = 52.7, 24.2 Hz).). ESI HRMS: [MH$^+$] calculated for $C_5H_{12}FN_2O$ 135.0934, found 135.0935.

4-Oxo-3,5-dioxa-4-thia-8,9-diazatricyclo[5.2.1.0^{2,6}]decane-8,9-dicarboxylic acid dibenzyl ester 28

To a cooled (0 °C) solution of compound **27** (200 mg, 0.5 mmol) in anhydrous THF (2.5 mL) was added DAST (75 µL, 0.56 mmol). The reaction mixture was stirred at room temperature for 1 h and quenched with an aqueous saturated solution of $NaHCO_3$. The aqueous layer was separated and extracted with AcOEt (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (cyclohexane/AcOEt 80:20) gave compound **28** as colourless oil (176 mg, 0.4 mmol, 79%, dr *endo/exo* 92:8). ^{1}H NMR (300 MHz, 323 K, $CDCl_3$) δ: 7.34 (m, 10H), 5.20 (br. s, 4H), 4.78 (br. s, 2H), 4.76 (br. s, 2H), 2.81 (d, J = 12.3 Hz, 1H), 1.76 (dm, J =

12.3 Hz, 1H). ^{13}C NMR (75 MHz, 323 K, $CDCl_3$) δ: 156.5, 135.4, 128.7, 128.6, 128.1, 85.9, 68.9, 61.1, 31.1. MS (ES): [MNa^+] 467, [MK^+] 483.

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Supporting Information Available: copies of ^1H, ^{19}F and ^{13}C NMR spectra. This material is free of charge via the Internet at http://pubs.acs.org

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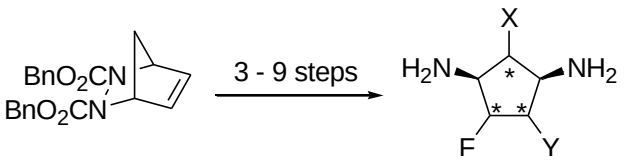
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