Oxidative desulfurization–fluorination of thioethers. Application for the synthesis of fluorinated nitrogen containing building blocks†‡

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An oxidative desulfurization–fluorination protocol has been used to synthesize (2*S*)-2-(difluoromethyl)-*N*-tosylpyrrolidine (**6a**) and (2*S*)-2-(trifluoromethyl)-*N*-tosylpyrrolidine (**7a**) from the (2*S*)-prolinol-derived (2*S*)-2-(4-chlorophenylthiomethyl)-*N*-tosylpyrrolidine (**9**) or (2*S*)-2-(dithian-2-yl)-*N*-tosylpyrrolidine (**5**). Efforts to prepare 3,3-difluoroalanine similarly from an *N*-protected *S*-aryl-cysteine ester **17** gave only traces of the target compound **18**. Instead, an unique *N*-(α,α-difluorobenzyl)-*N*-α′,α′-dibromoglycine ester **19** was formed by an unprecedented sequence of reaction steps. A plausible mechanism is suggested involving a sulfur-assisted deoxygenation-difluorination of an imino oxygen and a haloform reaction like carbon–carbon bond fission as key-steps. Efforts to prepare (2*S*)-2-(fluoromethyl)-*N*-tosylpyrrolidine (**12**) from (2*S*)-*N*-tosylprolinol (**3**) by treatment with Fluolead™ (1-*tert*-butyl-4-trifluorosulfanyl-3,5-dimethylbenzene) gave only 5% of the target compound, but 95% of (3*R*)-3-fluoro-*N*-tosylpiperidine (**11a**) by ring enlargement.

Introduction

Among others, amino acids, peptides and amines play important roles in biological processes. Since a couple of years medicinal chemists use specific fluorine substitution to modify the bioavailability and the metabolism of medicinally relevant compounds,[1] but also the affinity and selectivity of the interaction of small fluorinated molecules with biomacromolecules.[2,3]

The electron-withdrawing effect of a fluorine atom or a fluoroalkyl group modifies the pK_a of neighboring functions, and hence their character as hydrogen bond donors or acceptors. At lower pK_a protonation of amino functions becomes more difficult. The decreased basicity may alter the receptor affinity depending on whether the ligand acts in its neutral or in the protonated form. By way of example, MAO inhibitors were developed by applying the pK_a lowering effect of fluorine to amines, *e.g.* (*E*)-2-(3,4-dimethoxyphenyl)-3-fluoroallylamine was found to be an irreversible inhibitor of MAO with good MAO B selectivity.[4] The consequences of fluorine substitution on the MAO affinity and selectivity of fluorinated tranylcypromine derivatives have been extensively studied by our group.[5] Also the resorption properties of a molecule can be modified by the influence of fluorine atoms on the pK_a of neighboring ionizable functions and by lipophilicity effects. The uptake process of an ionizable drug depends on the respective proportions and lipophilicity of charged and neutral species. The introduction of fluorine atoms may allow modulation of the ionization of a molecule at physiological pH of 7.4. Thus, lowering of the pK_a of amines and nitrogen-containing heterocycles, by means of fluorinated substituents, can be a very important factor to facilitate the bioavailability, especially for oral administration of drugs.[6]

Therefore, the synthesis of fluorinated amines and amino acids is of particular interest.[7] Also different methods for the preparation of α,α-difluoro amino acids are known. The majority of these synthetic strategies apply building blocks for the introduction of difluoromethyl or difluoromethylene moieties. The most frequently used building block is the Reformatsky analogous reagent $BrZnCF_2CO_2Et$, which adds to aldehydes,[8–10] imines,[11,12] oxazolidines[13] or sulfinimines.[14,15] 2,2-Difluoromethylornithine (*elflornithine*) was synthesized from $CHClF_2$ and the resulting difluoro derivatives were then transformed to the *gem*-difluorinated amino acid.[16] In order to obtain L-4,4-difluoroglutamic acid *gem*-difluorinated precursors were synthesized by electrophilic fluorination with *N*-fluorobenzenesulfonimide (NSFI)[17] or by fluorination of (*R*)-2,3-*O*-isopropylidene glyceraldehydes with morpholino trifluorosulfurane (Morpho-DAST).[18] Attempts of direct nucleophilic fluorination of keto esters[19] with DAST only led to 20–31% of the difluorinated amino acids. By fluorodesulfurization reaction of cysteine with elemental fluorine, 33% of a mixture of 3-fluoro- and 3,3-difluoroalanine (92 : 8) was obtained.[20] Using trifluoromethyl fluoroxytrifluoromethane or perchlorylfluoride α,α-difluorinated β-amino acids were formed.[21,22] With SF_4 and DAST mono- and difluorination of protected amino acids with hydroxyl and oxo functions are possible.[23,24]

However, the described fluorination agents for the direct fluorination of amino acids are difficult to handle or did not lead selectively to the geminal difluorinated products. In this paper we report about the oxidative desulfurization–difluorination as a method for the preparation of α,α-difluoromethyl substituted amines and amino acids.

Results and Discussion

Fluoroalkylated pyrrolidine derivatives have been shown to be interesting for the development of new caspase inhibitors.[25,26]

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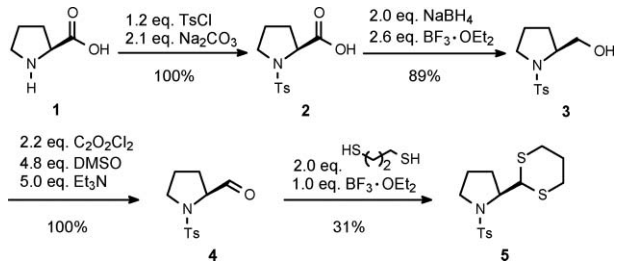
(2*S*)-2-(1,3-dithian-2-yl)-*N*-tosyl-pyrrolidine (**5**) seemed to be a suitable precursor for initial experiments to synthesize difluoromethyl substituted pyrrolidine derivatives by desulfurization–fluorination. Several protocols for similar reactions with different substrates have been published already[27] including our own results.[28] In a five step reaction sequence **5** was prepared from L-proline (**1**), which initially was *N*-protected with 4-toluenesulfonyl chloride and sodium bicarbonate. The formed *N*-tosyl-L-proline (**2**) was reduced to *N*-tosyl-prolinol (**3**) with sodium borohydride in the presence of borontrifluoride diethyl etherate. The alcohol **3** was converted to the aldehyde **4** by Swern-oxidation. Subsequent Corey–Seebach reaction with 1,3-propanedithiol led to the dithiane **5** with an overall yield of 27% (Scheme 1).



Scheme 1 Synthesis of (2*S*)-2-(1,3-dithian-2-yl)-*N*-tosylpyrrolidine (**5**).

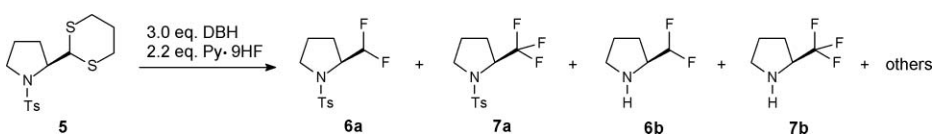
In order to synthesize the difluoromethyl substituted pyrrolidine **6a**, the dithiane **5** was reacted with DBH (3.0 equivalents) and Olah's reagent (2.2 equivalents) in dry dichloromethane. After work up and column chromatography the *gem*-difluoride **6a** was obtained as the major product (^{19}F NMR). The trifluoride **7a** and the *N*-deprotected difluorinated and trifluorinated proline derivatives **6b** and **7b** were detected as by-products (Table 1, entry 1). After treatment of the whole product mixture of entry 1 with tosylchoride in the presence of a base (entry 1a), (2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (**6a**) was obtained as the main product (90%, ^{19}F NMR) and (2*S*)-2-trifluoromethyl-*N*-tosylpyrrolidine (**7a**) as the only by-product (10%, ^{19}F NMR). The product mixture was isolated as a colorless waxy solid (61% yield of **6a**). Due to similar R_f-values the separation of the two substances by column chromatography was not possible.

Variation of the reaction conditions to 30 min at 0 °C and neutralization of the reaction mixture by column filtration through basic alumina led to a higher ratio of the trifluoride **7a** in the product mixture (entry 2). Again complete separation of the two compounds **6a** and **7a** was not possible, but the trifluoride **7a** could be obtained in an enriched mixture (**7a** : **6a** = 65 : 35, yield: 20%). After further optimization towards compound **7a**, may be by enhanced excess of Olah's reagent, this method is applicable for the preparation of compounds with potential biological relevance. The only yet published synthesis of (2*S*)-2-trifluoromethyl-*N*-tosylpyrrolidine (**7a**) was reported by Shustov *et al.*[29] The authors used a fluorodesoxygenation reaction of (*S*)-proline with SF_4 in HF giving 28% of **7a**. For this reaction a steel autoclave, as well as special equipment for the handling with SF_4 and HF are necessary. A further disadvantage of this reaction was the long reaction time of 8 h. In contrast our synthesis can be performed in simple PTFE-flasks and shows a complete conversion of **5** within 30 min at 0 °C.

Good selectivity for **6a** was observed at room temperature (entries 3 and 4) but at longer reaction time 29% of several not identified fluorinated by-products were formed (^{19}F NMR). Structural assignment of (2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (**6a**) was difficult on a first view because of the different coupling patterns of the two diastereotopic fluorine atoms F1 and F2 (see Fig. 1). Fluorine atom F1 has a chemical shift of $\delta = -122.6$ ppm and splits to a four-line AB-spectrum, without a vicinal F,H-coupling, while F2 forms an AB-spectrum with eight lines at $\delta = -136.8$ ppm induced by an additional $^3J_{F,H} = 25.3$ Hz by coupling with the proton of the CH-group of the proline ring. The arrangement of the difluoromethyl moiety can also be confirmed by the coupling of the CH-proton of the proline ring in the ^{1}H NMR spectrum. This proton shows a coupling pattern of a dublett of a multiplett with only one H,F-coupling of $^3J_{H,F} = 25.6$ Hz at $\delta =$ 3.79 ppm.

The different coupling pattern of the fluorine atoms is probably caused by the preferred conformation of the compound shown in Fig. 1. The difluoromethyl group is arranged in such a way that the dihedral angel between F1 and the proton of the CH-group of the proline ring is perpenticular and consequently no coupling of these two nuclei can be observed. The second fluorine atom F2 is located in a *gauche* position to the proline proton and shows a coupling constant of $^3J_{F,H} = 25.3$ Hz. The structure shown in Fig. 1 was geometry optimized by quantum chemical calculation (B3LYP/6-311+G(2d,2p)). The calculation did not exhibit an exact orthogonal geometry of one fluorine atom to the β-proton.

Table 1 Oxidative desulfurization–difluorination reactions of dithianen **5**



Entry	DBH (eq.)	Py·9HF (eq.)	Reaction conditions	Crude Product Mixture (^{19}F NMR,%) 6a	6b	7a	7b	others
1[a]	3.0	2.2	–78 °C; 30 min, –60 °C; 1 h, 0 °C; 30 min, r.t.	59	30	8	3	—
2	3.0	2.2	30 min, 0 °C (Alumina)	56	—	44	—	—
3	3.0	2.2	30 min, r.t. (Alumina)	95[b]	—	5[b]	—	—
4	3.0	2.2	20 h, r.t.	65	—	6	—	29

[a] After tosylation of the whole product mixture of entry 1 a 90 : 10 mixture (^{19}F NMR) of **6a** and **7a** was found. [b] After column chromatography.

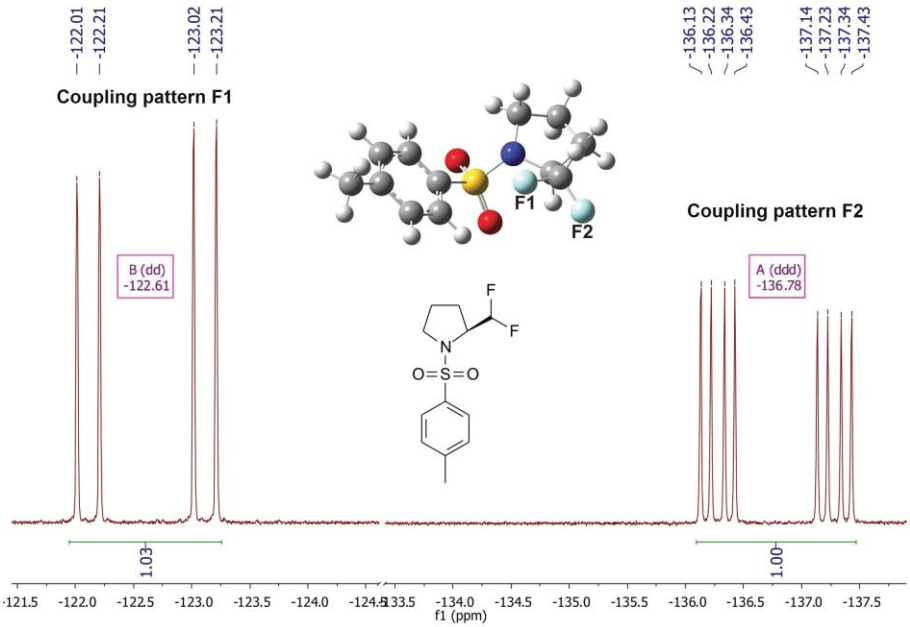
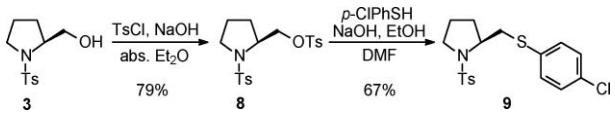


Fig. 1 Coupled ^{19}F NMR spectra of (2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (**6a**).

The formation of the *gem*-difluoro compound **6a** can be formulated analogously to the fluorodesulfurization mechanism of dithianes postulated by Katzenellenbogen *et al.*[27b] The probable mechanism of the formation of the trifluoride **7a** is analogous to the one postulated in our previous work.[28]

In order to avoid the five-step preparation of (2*S*)-*N*-tosyl-2-(dithian-2-yl)pyrrolidine (**5**), we intended to apply an oxidative desulfurization–difluorination approach[28,30] for the synthesis of (2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (**6a**). Therefore, (2*S*)-(4-chlorophenylthiomethyl)-*N*-tosylpyrrolidine (**9**) was prepared from *N*-tosyl-L-prolinol (**3**) by *O*-tosylation to form **8** and subsequent nucleophilic substitution of the tosylate with *p*-chlorothiophenol (Scheme 2). The formed thioether **9** was then used as a starting material for fluorination.



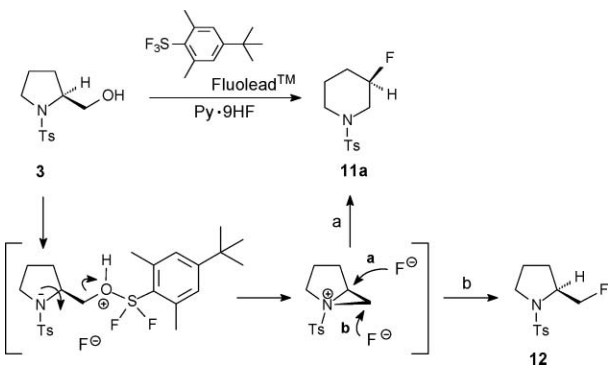
Scheme 2 Synthesis of (2*S*)-(4-chlorophenylthiomethyl)-*N*-tosylpyrrolidine (**9**).

Applying our standard oxidative desulfurization–difluorination conditions,[28] **9** was reacted with 3 equivalents of DBH and 6 equivalents of Py·9HF in dry CH_2Cl_2 at room temperature for 17 h (Table 2, entry 1). Filtration of the product mixture over basic alumina and column chromatography (silica gel) afforded (2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (**6a**) as a waxy colorless substance with 33% yield. Additionally, (2*S*)-2-dibromofluoromethyl-*N*-tosylpyrrolidine (**10**) (13%) and the 3-fluoro-piperidine derivative **11a** (16%), were isolated. Lowering the amount of both the electrophile and the fluorinating reagent to 2 equivalents of DBH and 3 equivalents of Olah's reagent caused the preferred formation of the *gem*-dibromofluoride **10**. The *gem*-difluoride **6a** (15%) was detected as a by-product (entry 2). With 2 equivalents of DBH and 4 equivalents of Py·9HF the *gem*-dibromofluoride **10** was formed almost exclusively and (2*S*)-2-fluoromethyl-*N*-tosylpyrrolidine (**12**) was detected as the only by-product (entry 3, for the mechanism of formation see ref. 28b).

In contrast, increasing the amount of the fluorinating reagent to 9 equivalents in combination with 3 equivalents of DBH led preferably to the fluorinated piperidine derivative **11b**, which is *meta*-brominated at the tosyl ring. In addition, a small amount of dibromofluoride **10** was identified.

Compounds **6a, 7a**, and **10** are formed by initial fluoro-Pummerer reaction(s) and subsequent desulfurization–fluorination or –bromination as discussed earlier for similar transformations of a variety of alkyl aryl thioethers.[28]

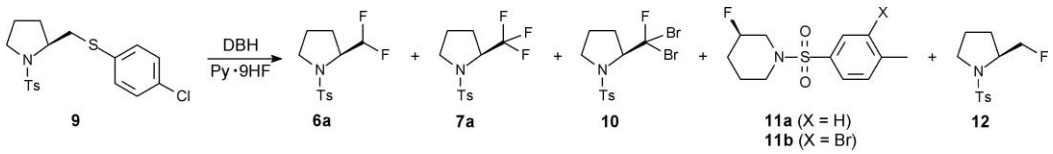
(3*R*)-3-Fluoro-*N*-tosylpiperidine (**11a**) itself could be synthesized selectively from *N*-tosyl-L-prolinol (**3**) using the new fluorinating reagent[31] Fluolead™ (2 equivalents) and Olah's reagent (0.22 equivalents) with an isolated yield of 95% (Scheme 3).



Scheme 3 Mechanism of the conversion of **3** with Fluolead™ and Olah's reagent.

The formation of **11a** proceeds *via* a ring expansion reaction similar to the one proposed by Shreeve *et al.*[32] and Cossy

Table 2 Oxidative desulfurization–difluorination of (2*S*)-2-(4-chlorophenylthiomethyl)-*N*-tosylpyrrolidine (**9**)



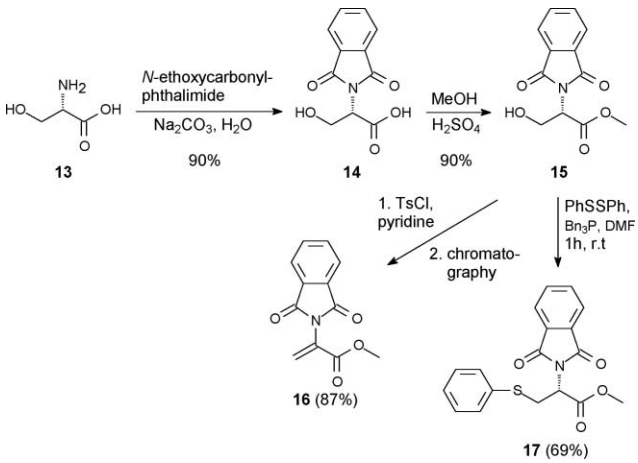
Entry	DBH (eq.)	Py·9HF (eq.)	Reaction Conditions	Crude Product Mixture (^{19}F NMR,%) 6a	7a	10	11a/11b	12
1	3.0	6.0	17 h, r.t.	54	2	14	31[a]	—
2	2.0	3.0	17 h, r.t.	15	—	85	—	—
3	2.0	4.0	17 h, r.t.	—	—	90	—	10
4	3.0	9.0	17 h, r.t.	1	—	7	92[b]	—

[a] 3-fluoro-*N*-tosylpiperidine (**11a**). [b] 3-fluoro-*N*-(3-bromotoluenesulfonyl)piperidine (**11b**)

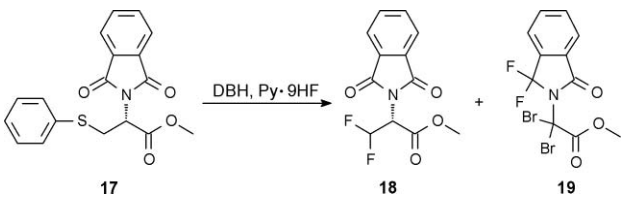
et al.[33] for reactions of prolinol derivatives, which with DAST or desoxofluor™ lead to mixtures of optical active fluoro pyrrolidine and fluoro piperidine derivatives. The selectivity of these rearrangements depended on the substituents at the pyrrolidine ring and steric constrains on nitrogen. Using Fluolead™ as a fluorinating agent we detected only 5% of the not rearranged product (2*S*)-2-fluoromethyl-*N*-tosylpyrrolidine (**12**) in the product mixture (^{19}F NMR). Thus, the selectivity and the yield (95% of **11a**) of this reaction are much better than most of the reactions described in literature.[32,33]

The oxidative desulfurization–difluorination might also be an opportunity for the direct difluorination of amino acids in β-position starting from suitably substituted amino acids such as *S*-phenylcysteine derivatives. In order to prepare 3,3-difluoroalanine on an alternative pathway to the use of fluorinated building blocks,[34–37] or fluorinating reagents like fluoroxytrifluoromethane or elemental fluorine[20] we synthesized methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(phenylthio)propanoate (**17**) as a precursor for an oxidative desulfurization–difluorination reaction in a three step protocol starting from L-serine. After protection of the amino function with *N*-ethoxycarbonylphthalimide and Na_2CO_3 to form **14** the carbonyl function was esterified with methanol to yield **15**. The hydroxyl function was scheduled to be converted to a tosyl group. Unfortunally, elimination of toluenesulfonic acid to **16**[38] took place during purification on silica gel or basic alumina due to the high acidity of the proton in α-position of the nitrogen. Finally, the reaction of **15** with Hata's reagent (diphenyldisulfide and tributylphosphine)[39] afforded the target compound, methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(phenylthio)propanoate (**17**), in 69% yield (Scheme 4).

In the next reaction step, **17** was subjected to the standard conditions of the oxidative desulfurization–difluorination (3 equivalents DBH, 6 equivalents Py·9HF).[28] However, the expected difluorinated product, methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3,3-difluoropropanoate (**18**), was only verified as a by-product by ^{19}F NMR spectroscopy and ESI mass spectrometry (Scheme 5). The major product of the reaction was isolated by column chromatography on neutral alumina. Initially, no structure could be proposed due to the lack of indicative signals in ^{1}H, ^{13}C, and ^{19}F NMR spectra for structure elucidation. Finally, repeated recrystallization from pentane–diethyl ether led to crystals suitable for X-ray crystallographic analysis. According to these data, the product was identified as the α,α-dibromo-α′,α′-difluoroalkylamide **19** (Fig. 2). The amide nitrogen is flanked by a difluoromethylene group on the one and a dibromomethylene moiety on the other side. This structure unit to the best of our knowledge was not known in literature before.



Scheme 4 Synthesis of methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(phenylthio)propanoate (**17**).



Scheme 5 Oxidative desulfurization–difluorination reaction of **17**.

This particular product necessitated some considerations about its formation from **17**. The formal exchange of a carboxyl oxygen atom as part of an imino group by two fluorine atoms with DBH and Olah's reagent was not observed till now. Generally fluorinating agents like SF_4, DAST or desoxofluor™ are necessary for the direct transformation of carbonyl oxygen atoms to *gem* difluorides.[40,41] Also the introduction of two bromine atoms in α-position of the nitrogen of an amino acid formally replacing an arylthiomethyl moiety was not described yet.

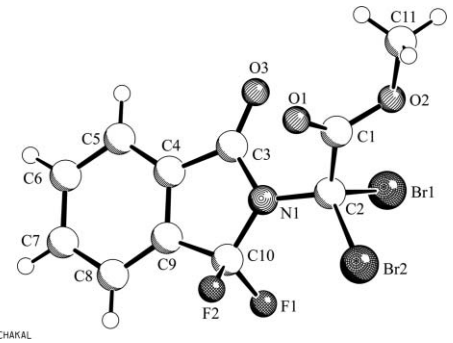


Fig. 2 X-ray structure of methyl 2,2-dibromo-2-(1,1-difluoro-3-oxoisoindolin-2-yl)acetate (**19**).

Thus, we speculated about a plausible mechanism of formation of the α,α-dibromo-α′,α′-difluoroamide **19** (Scheme 6). Initially, the sulfur is attacked by the electrophile DBH (Br^+) to form intermediate **I**. Due to the close proximity of the sulfenium ion center to one of the phthalimide oxygens, nucleophilic attack of the oxygen on sulfur can occur, analogously to the reaction of a ketone with DAST, whereupon *via* an oxonium ion the stabilized carbenium ion **II** can be formed. The carbenium ion **II** can add a fluoride from the fluorinating reagent forming a carbon flanked by fluorine, oxygen and an imide nitrogen. This strongly electrophilic carbon is attacked again by a fluoride. By breaking the carbon-oxygen bond, bromide is eliminated and the sulfoxide, methyl (2*S*)-2-(1,1-difluoro-3-oxoisoindolin-2-yl)-3-(phenylsulfinyl)propanoate (**20**) is formed.

The two bromine atoms might be introduced subsequently on the following way: A second bromonium ion attacks sulfur to form the cation **III**. HBr elimination from **III** leads to the carbenium/sulfoxonium ion **IV**, from which the olefin **21** is formed by deprotonation. Addition of Br_2 or "BrF" to the double bond of **21**, elimination of hydrogen bromide and again addition of "BrX" to the double bond leads to the trihalogen moiety of **22**. In the course of a "haloform" reaction a dihalogenmethyl sulfinyl anion is eliminated simultaneously with the attack of a bromide on **22** to obtain the α,α-dibromo-α′,α′-difluoroalkylamide **19**. Alternative mechanisms are possible, but seem less probable.[42]

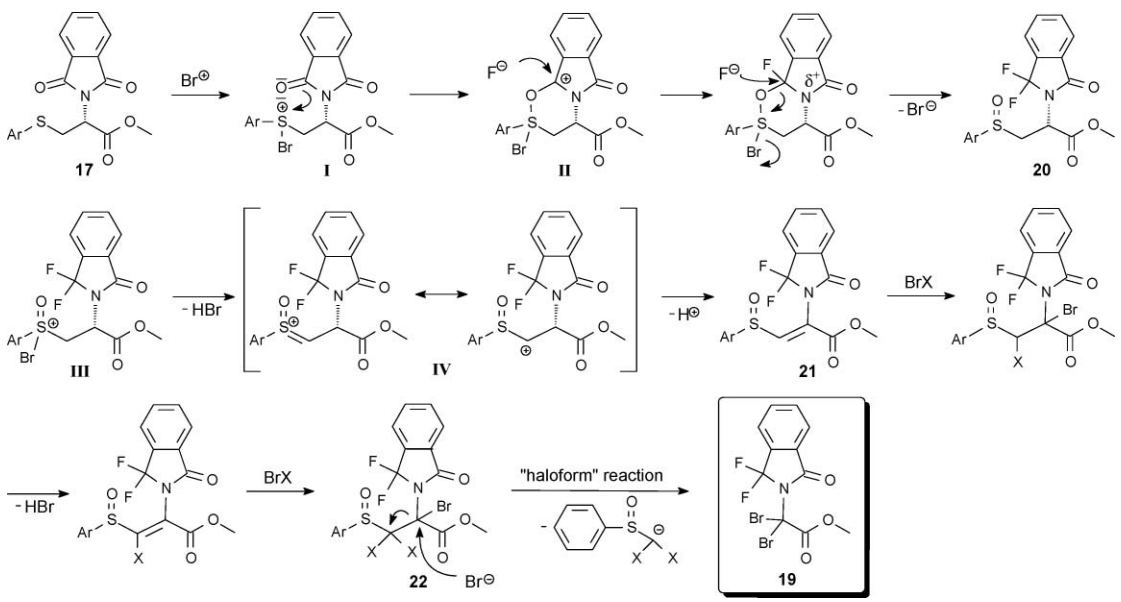
Conclusion

Up to present there were no simple methods known for the synthesis of (2*S*)-2-difluoromethylpyrrolidine derivatives. Starting from (2*S*)-2-(dithian-2-yl)-*N*-tosylpyrrolidine (**5**) the selective synthesis of (2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (**6a**) (61% yield), besides a minor amount of (2*S*)-2-trifluoromethyl-*N*-tosylpyrrolidine (**7a**), was successful by conversion with DBH and Py·9HF. The product ratio was not significantly changed by modified reaction conditions. The share of (2*S*)-2-trifluoromethyl-*N*-tosylpyrrolidine (**7a**) could be slightly increased under the conditions shown in Table 1, entry 2. Complete separation of the two fluorinated pyrrolidine derivatives was not possible.

(2*S*)-2-Difluoromethyl-*N*-tosylpyrrolidine (**6a**) was also synthesized by the oxidative desulfurization–difluorination approach starting from 2-(arylthiomethyl)pyrrolidine **9**, however with only 33% yield. Despite the low yield this protocol provides a similar overall yield like the multi-step method *via* the dithiane **5** (17% or 19%, respectively).

Lowering the amounts of electrophile and fluorinating reagent led exclusively to the dibromofluoride **10**. Increasing the amount of Olah's reagent implicated the formation of the ring expanded monofluoro substituted piperidine **11b**, monobrominated in *meta*-position at the tosyl group. The reaction of *N*-tosyl-L-prolinol (**3**) with Fluolead™ and Olah's reagent delivered the (3*R*)-3-fluoro-*N*-tosylpiperidine (**11a**) in 95% yield by ring enlargement.

Under the conditions of the desulfurization–difluorination reaction with DBH and Olah's reagent of methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(phenylthio)propanoate (**17**) the expected 3,3-difluoroalanine derivative **18** was formed only as a by-product. The reaction led mainly to a unique, so far not known structure motiv of an α,α-dibromo-α′,α′-difluoroalkylamide **19**. The



Scheme 6 Plausible mechanism of formation of the α,α-dibromo-α′,α′-difluoroamide **19**.

formation of this product seems to be caused by the close proximity of one of the carboxyl oxygens of the phthalimide moiety to the sulfur initiating a fluoro-Pummerer-like rearrangement.

Experimental

General methods

Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). NMR spectra were recorded on a Bruker ARX300 and a Bruker DPX300 (^{1}H NMR, 300 MHz, ^{13}C NMR, 75 MHz, ^{19}F NMR, 282 MHz), Bruker AMX 400 (^{1}H NMR, 400 MHz, ^{13}C NMR, 100 MHz) and Varian Inova (^{1}H NMR, 500 MHz, ^{13}C NMR, 126 MHz, ^{19}F NMR, 470 MHz) spectrometers. TMS (^{1}H), $CDCl_3$ (^{13}C) and $CFCl_3$ (^{19}F) were used as internal standards. Mass spectra were recorded on Thermo-Finningan MAT8200 (EI, 70 eV), Waters–Micromass GCT (GCToF, EI), and Waters–Micromass Quatromicro GC (GC/CI and EI, 70 eV) instruments. All air and moisture-sensitive reactions were performed under argon atmosphere. Solvents were purified and dried by literature methods where necessary. The reactions with Olah's reagent were performed in Teflon™ flasks. The alkyl aryl thioethers were prepared from the corresponding thiophenols and alkyl halides under basic conditions.[43]

Synthesis of (2*S*)-2-(dithian-2-yl)-*N*-tosylpyrrolidine (5)

N-Tosyl-L-proline (**2**) (100%) and *N-tosyl-L-prolinol* (**3**) (89%) were prepared according to literature procedures.[44] *N-Tosyl-L-prolinal* (**4**) was synthesized by Swern-oxidation in a 23.0 mmol scale (5.83 g, 100%) and isolated as a yellow solid; mp 117 °C with decomposition (lit.,[45] 139–141 °C); $[\alpha]_D^{20}$ −102.0 (*c* 1.03 in $CHCl_3$) (lit.,[45] $[\alpha]_D^{20}$ −121.0 (*c* 1.00 in MeOH). The spectroscopic data match with those given in literature.[45]

(2*S*)-2-(*dithian-2-yl*)-*N-tosylpyrrolidine* (**5**) was synthesized by Corey–Seebach reaction according to the literature procedure in a 5.87 mmol scale.[46] The product was purified by column chromatography (silica gel, cyclohexane/ethyl acetate, 4 : 1) and obtained as a yellowish solid (624 mg, 31%); mp 97 °C; $[\alpha]_D^{20}$ −72.3 (*c* 0.98 in $CHCl_3$); δ_H (300 MHz; $CDCl_3$, TMS): 1.44 (1 H, m, CH_2), 1.69 (1 H, m, $CHCH_2$), 1.76–1.94 (2 H, m, CH_2), 2.07–2.18 (2 H, m, CH_2), 2.43 (3 H, s, CH_3), 2.82–3.00 (4 H, m, SCH_2), 3.20 (1 H, m, NCH_2), 3.39 (1 H, m, NCH_2), 3.88 (1 H, m, NCH), 4.74 (1 H, d, $^3J_{H,H}$ = 4.0 Hz, SCHS), 7.32 (2 H, d, $^3J_{H,H}$ = 8.0 Hz, Ph-CH), 7.76 (2 H, d, $^3J_{H,H}$ = 8.3 Hz, Ph-CH); δ_C (75 MHz; $CDCl_3$): 21.5 (CH_3), 24.9 (CH_2), 26.2 (CH_2), 28.2 ($CHCH_2$), 30.1 (SCH_2), 30.9 (SCH_2), 49.8 (NCH_2), 54.3 (SCHS), 62.6 (NCH), 127.6 (Ph-CH), 129.7 (Ph-CH), 134.4 (Ph-C), 143.5 (Ph-C). MS (EI-GC-inlet): *m/z* (%) 343 (<0.1) [M$^+$], 224 (100) [$C_{11}H_{14}NO_2S^+$], 155 (24) [$C_7H_7O_2S^+$], 119 (10) [$C_4H_7S_2^+$], 91 (67) [$C_7H_7^+$]. Exact mass (ESI): [M+Na$^+$] calcd for $C_{18}H_{26}FNO_5SNa^+$: 366.0632; found: 366.0625. Anal. calcd. for $C_{15}H_{21}NO_2S_3$: C, 52.44; H, 6.16; N, 4.08. Found: C, 52.11; H, 5.94; N, 3.99.

Conversion of (2*S*)-2-(dithian-2-yl)-*N*-tosylpyrrolidine (5) with DBH and Olah's reagent

Synthesis of (2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (6a) (Table 2, entry 1). 5,5-Dimethyl-1,3-dibromohydantoin (DBH, 172 mg, 0.60 mmol, 3.0 eq.) was dissolved in dry dichloromethane (4 cm^3) under argon in a flame dried PTFE-flask and cooled to −78 °C. Then Olah's reagent (0.10 cm^3, 0.44 mmol, 2.2 eq.) was dropped slowly to the reaction mixture. Subsequently **5** (69 mg, 0.20 mmol), dissolved in dry dichloromethane (2 cm^3), was dropped to the reaction mixture within 10–15 min. The mixture was stirred for 30 min at −60 °C, 1 h at 0 °C and 30 min at room temperature. Afterwards it was cooled down to 0 °C and neutralized with ice-cold saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with dichloromethane (3 × 4 cm^3) and the combined organic layer was washed with 1 N HCl, 5% aqueous $NaHCO_3$ and brine (2 × 5 cm^3) and dried over anhydrous $MgSO_4$. After concentration under reduced pressure, the products were separated by column chromatography (silica gel, pentane–diethyl ether, 10 : 1). The main product of this reaction was the tosyl protected (2*S*)-2-difluoromethylpyrrolidine derivative **6a**. As by-products the deprotected (2*S*)-2-difluoromethylpyrrolidine (**6b**) and the *N*-protected and the deprotected (2*S*)-2-trifluoromethyl pyrrolidine derivatives **7a** and **7b** were found.

In a second attempt, the whole product mixture was subjected to tosylation according to the method given in ref. [44] (Table 1, entry 1a). Under these conditions **6a** was the main product (90%, ^{19}F NMR) and **7a** (10%, ^{19}F NMR) was the only by-product. Column chromatographic separation of the by-product was not possible. The product mixture was obtained as a colorless wax (yield calculated for **6a**: 34 mg, 61%).

(2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (6a). $[\alpha]_D^{20}$ −38.7 (*c* 0.70 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$ TMS): 1.50–1.67 (2 H, m, CH_2 & $CHCH_2$), 1.92 (1 H, m, CH_2), 2.10 (1 H, m, $CHCH_2$), 2.45 (3 H, s, CH_3), 3.15 (1 H, m, NCH_2), 3.47 (1 H, m, NCH_2), 3.79 (1 H, dm, $^3J_{H,F}$ = 25.6 Hz, NCH), 6.11 (1 H, ddd, $^2J_{H,F}$ = 57.9 Hz, $^2J_{H,F}$ = 55.0 Hz, $^3J_{H,H}$ = 1.6 Hz, CF_2H), 7.35 (2 H, d, $^3J_{H,H}$ = 8.0 Hz, Ph-CH), 7.73 (2 H, m, $^3J_{H,H}$ = 8.3 Hz, Ph-CH); δ_C (126 MHz, $CDCl_3$): 21.6 (CH_3), 24.3 (d, $^3J_{C,F}$ = 4.3 Hz, $CHCH_2$), 24.6 (d, $^4J_{C,F}$ = 2.1 Hz, CH_2), 49.3 (NCH_2), 60.0 (dd, $^2J_{C,F}$ = 31.8 Hz, $^2J_{C,F}$ = 22.5 Hz, NCH), 115.8 (dd, $^1J_{C,F}$ = 247.6 Hz, $^1J_{C,F}$ = 241.7 Hz, CF_2H), 127.6 (Ph-CH), 129.9 (Ph-CH), 133.7 (Ph-C), 144.1 (Ph-C); δ_F (282 MHz, $CDCl_3$, $CFCl_3$): −122.6 (1 F, dd, $^2J_{F,F}$ = 283.5 Hz, $^2J_{H,F}$ = 54.9 Hz), −136.9 (1 F, ddd, $^2J_{F,F}$ = 283.4 Hz, $^2J_{H,F}$ = 58.0 Hz, $^3J_{H,F}$ = 25.3 Hz). MS (EI-GC-inlet): *m/z* (%) 275 (<0.1) [M$^+$], 224 (59) [$C_{11}H_{14}NO_2S^+$], 155 (40) [$C_7H_7O_2S^+$], 91 (100) [$C_7H_7^+$], 65 (44), 41 (19) [$C_3H_5^+$]. Exact mass (ESI): [M+Na$^+$] calcd for $C_{12}H_{15}F_2NO_2SNa^+$: 298.0684; found: 298.0680.

Synthesis of (2*S*)-2-trifluoromethyl-*N*-tosylpyrrolidine (7a) (Table 2, entry 2). DBH (412 mg, 1.44 mmol, 3.0 eq.) was dissolved in dry dichloromethane (3 cm^3) under argon in a flame dried PTFE-flask and cooled to 0 °C. Olah's reagent (0.24 cm^3, 1.06 mmol, 2.2 eq.) and **5** (165 mg, 0.48 mmol), dissolved in dry dichloromethane, were given dropwise to the reaction mixture. The mixture was stirred 30 min at 0 °C and dichloromethane (20 cm^3) was added. Then the entire mixture was given to a PE-column filled with basic alumina (2 × 10 cm, ca 50 g) for neutralization. The filtrate was collected, the column was rinsed with dichloromethane (20 cm^3), the dichloromethane phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. After column chromatography (silica gel, cyclohexane/ethyl acetate, 20 : 1) the trifluoride **7a** (65%, ^{19}F NMR) was obtained in a mixture with the difluoride **6a** as the only by-product (35%, ^{19}F NMR) as a colorless oil (yield calculated for **7a**: 14 mg, 20%).

(2*S*)-2-trifluoromethyl-*N*-tosylpyrrolidine (7a). $[\alpha]_D^{20}$ −38.0 (*c* 0.67 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$, TMS): 1.74 (1 H, m, $CHCH_2$), 1.86 (1 H, m, CH_2), 1.97 (1 H, m, $CHCH_2$), 2.07 (1 H, m, CH_2), 2.44 (3 H, s, CH_3), 3.33 (1 H, m, NCH_2), 3.49 (1 H, m, NCH_2), 4.42 (1 H, m, NCH), 7.35 (2 H, d, $^3J_{H,F}$ = 8.0 Hz, Ph-CH), 7.74 (2 H, d, $^3J_{H,F}$ = 8.4 Hz, Ph-CH); δ_C (126 MHz, $CDCl_3$): 21.5 (CH_3), 26.4 (CH_2), 29.3 (CH_2CH), 49.1 (NCH_2), 59.7 (q, $^2J_{C,F}$ = 32.0 Hz, NCH), 125.2 (q, $^1J_{C,F}$ = 281.6 Hz, CF_3), 127.5 (Ph-CH), 129.8 (Ph-CH), 133.8 (Ph-C), 143.8 (Ph-C); δ_F (282 MHz, $CDCl_3$, $CFCl_3$): –75.7 (3 F, d, $^3J_{H,F}$ = 7.6 Hz). MS (EI-GC-inlet): *m*/*z* (%) 293 (6) [M^+], 224 (70) [$C_{11}H_{14}NO_2S^+$], 155 (51) [$C_7H_7O_2S^+$], 91 (100) [$C_7H_7^+$], 65 (37), 41 (19) [$C_3H_5^+$]. Exact mass (ESI): [M+Na^+] calcd for $C_{12}H_{14}F_3NO_2SNa^+$: 316.0590; found: 316.0584.

Synthesis of (2*S*)-2-(4-chlorophenylthiomethyl)-*N*-tosylpyrrolidine (9)

***N*,*O*-Bis-tosyl-L-prolinol (8)[47].** A suspension of *N*-tosyl-L-prolinol (**3**) (2.838 g, 11.13 mmol) in dry diethyl ether (16 cm^3) was cooled to 0 °C. *p*-Toluenesulfonyl chloride (2.122 g, 11.13 mmol, 1.0 eq.) and powdered sodium hydroxide (533 mg, 13.35 mmol, 1.2 eq.) were added and the mixture was stirred at 0 °C for 1 h. Stirring was continued over night at room temperature. Then ice water was added (30 cm^3) and the aqueous phase was extracted with diethyl ether (3 × 20 cm^3). The combined organic layer was washed with water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After column chromatography (silica gel, cyclohexane/ethyl acetate, 6 : 1) the product **8** was obtained as a white solid (3.168 g, 79%); mp 100 °C; $[\alpha]_D^{20}$ −119.3 (*c* 1.00 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$, TMS): 1.50–1.70 (2 H, m, $CHCH_2$), 1.73–1.93 (2 H, m, CH_2), 2.43 (3 H, s, CH_3), 2.47 (3 H, s, CH_3), 3.04 (1 H, m, NCH), 3.39 (2 H, m, NCH_2), 3.75 (1 H, m, NCH_2), 3.95 (1 H, dd, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 8.2 Hz, $CHCH_2O$), 4.25 (1 H, dd, $^2J_{H,H}$ = 9.9 Hz, $^3J_{H,H}$ = 3.6 Hz, $CHCH_2O$), 7.31 (2 H, d, $^3J_{H,H}$ = 8.0 Hz, Ph-CH), 7.38 (2 H, d, $^3J_{H,H}$ = 8.0 Hz, Ph-CH), 7.66 (2 H, d, $^3J_{H,H}$ = 8.3 Hz, Ph-CH), 7.82 (2 H, d, $^3J_{H,H}$ = 8.3 Hz, Ph-CH); δ_C (101 MHz, $CDCl_3$): 21.5 (CH_3), 21.7 (CH_3), 23.7 (CH_2), 28.5 (CH_2CH), 49.3 (NCH_2), 57.6 (NCH), 71.5 ($CHCH_2O$), 127.6 (Ph-CH), 128.0 (Ph-CH), 129.8 (Ph-CH), 130.0 (Ph-CH), 132.6 (Ph-C), 133.5 (Ph-C), 143.9 (Ph-C), 145.0 (Ph-C). Exact mass (ESI): [M+H^+] calcd for $C_{19}H_{23}NO_5S_2H^+$: 410.1090; found: 410.1095. Exact mass (ESI): [M+Na^+] calcd for $C_{19}H_{23}NO_5S_2Na^+$: 432.0910; found: 432.0916. Anal. calcd. for $C_{19}H_{23}NO_5S_2$: C, 55.72; H, 5.66; N, 3.42. Found: C, 55.61; H, 5.51; N, 3.44.

(2*S*)-2-(4-Chlorophenylthiomethyl)-*N*-tosylpyrrolidine (9). According to the literature procedure *N*,*O*-bis-tosyl-L-prolinol (**8**) (1.638 g, 4.00 mmol) was reacted with *p*-chlorothiophenol (608 mg, 4.22 mmol).[43] Then the reaction mixture was diluted with water (300 cm^3) and extracted with ethyl acetate (3 × 50 cm^3). The combined organic layer was washed with water, saturated $NaHCO_3$ solution and brine (2 × 50 cm^3), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After column chromatography (silica gel, cyclohexane/ethyl acetate, 8 : 1) the product was obtained as a colorless oil, that crystallized at friction (1.027 g, 67%); mp 67 °C; $[\alpha]_D^{20}$ −311.1 (*c* 0.98 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$, TMS): 1.46–1.70 (2 H, m, $CHCH_2$), 1.71–1.94 (2 H, m, CH_2), 2.41 (3 H, s, CH_3), 2.77 (1 H, dd, $^2J_{H,H}$ = 13.4 Hz, $^3J_{H,H}$ = 10.4 Hz, $CHCH_2S$), 3.03 (1 H, m, NCH), 3.57 (2 H, m, NCH_2), 3.64 (1 H, m, $CHCH_2S$), 7.26 (2 H, d, $^3J_{H,H}$ = 8.0 Hz, Ph-CH), 7.32 (2 H, d, $^3J_{H,H}$ = 8.9 Hz, Ph-CH), 7.40 (2 H, d, $^3J_{H,H}$ = 8.9 Hz, Ph-CH), 7.55 (2 H, d, $^3J_{H,H}$ = 8.3 Hz, Ph-CH); δ_C (101 MHz, $CDCl_3$): 21.5 (CH_3), 23.7 (CH_2), 30.2 (CH_2CH), 38.5 ($CHCH_2S$), 49.7 (NCH_2), 58.7 (NCH), 127.4 (Ph-CH), 129.1 (Ph-CH), 129.7 (Ph-CH), 130.2 (Ph-CH), 131.9 (Ph-C), 133.7 (Ph-C), 133.9 (Ph-C), 143.6 (Ph-C). MS (EI-GC-inlet): *m*/*z* (%) 381 (6) [M^+], 224 (100) [$C_{11}H_{14}NO_2S^+$], 155 (71) [$C_7H_7O_2S^+$], 91 (38) [$C_7H_7^+$], 45 (6) [$C_2H_4O^+$]. Exact mass (ESI): [M+H^+] calcd for $C_{18}H_{20}ClNO_2S_2H^+$: 382.0697; found: 382.0706; [M+Na^+] calcd for $C_{18}H_{20}ClNO_2S_2Na^+$: 404.0516; found: 404.0528. Anal. calcd. for $C_{18}H_{20}ClNO_2S_2$: C, 56.60; H, 5.28; N, 3.67. Found: C, 56.48; H, 4.98; N, 3.67.

Oxidative desulfurization–difluorination of thioethers

General procedure[28]

Olah's reagent was added to a solution of the corresponding thioether (0.5 mmol) in dry dichloromethane (5 cm^3) in a Teflon™ flask *via* a polypropylene/polyethylene syringe. DBH was added and the mixture was stirred for 17 h at room temperature. For the particular equivalents of Olah's reagent and DBH see Table 2.

Oxidative desulfurization–difluorination of (2*S*)-2-(4-chlorophenylthiomethyl)-*N*-tosylpyrrolidine (9). According to the general procedure, (2*S*)-2-(4-chlorophenylthiomethyl)-1-tosylpyrrolidine (**9**) (191 mg, 0.5 mmol) was reacted with Olah's reagent (0.69 cm^3, 3.0 mmol, 6 eq.) and DBH (431 mg, 1.5 mmol, 3 eq.) in dry dichloromethane (5 cm^3) for 17 h at room temperature. Then the reaction mixture was passed through a short PE-column with basic alumina for neutralization and the column was rinsed with dichloromethane (100 cm^3). The organic layer was collected in two fractions. The first fraction contained a mixture of the difluoromethyl, trifluoromethyl and dibromofluoromethyl substituted pyrrolidine derivatives **6a**, **7a** and **10** as well as the monofluorinated piperidine **11a**. The second fraction contained pure (3*R*)-fluoro-*N*-tosylpiperidine (**11a**). Repeated column chromatography of the first fraction (silica gel, pentane: 1.000cm^3; then pentane–diethyl ether, 3 : 1) delivered the difluormethyl product **6a** and the dibromofluoromethyl derivative **10**.

(2*S*)-2-Difluoromethyl-*N*-tosylpyrrolidine (6a). Isolated as a colorless waxy solid (45 mg, 33%); mp 76–77 °C; $[\alpha]_D^{20}$ −40.7 (*c* 0.85 in $CHCl_3$). The spectroscopic data are matching to those given above.

(2*S*)-2-Dibromofluoromethyl-*N*-tosylpyrrolidine (10). Isolated as a colorless oil (68 mg, 33%). Also obtained as main product of the reactions of entry 2 (0.25 mmol scale, 56 mg, 54%) and 3 (0.25 mmol scale, 65 mg, 63%) in Table 2; $[\alpha]_D^{20}$ −112.9 (*c* 0.93 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$, TMS): 1.50–1.61 (2 H, m, CH_2), 2.00 (1 H, m, CH_2), 2.12 (1 H, m, $CHCH_2$), 2.23 (1 H, m, $CHCH_2$), 2.45 (3 H, s, CH_3), 3.15 (1 H, m, NCH_2), 3.46 (1 H, m, NCH_2), 4.77 (1 H, ddd, $^3J_{H,F}$ = 11.0 Hz, $^3J_{H,H}$ = 8.7 Hz, $^4J_{H,H}$ = 4.9 Hz, NCH), 7.33 (2 H, d, $^3J_{H,H}$ = 8.0 Hz, Ph-CH), 7.76 (2 H, d, $^3J_{H,H}$ = 8.3 Hz, Ph-CH); δ_C (126 MHz, $CDCl_3$): 21.6 (CH_3), 25.0 (CH_2), 30.3 (d, $^3J_{C,F}$ = 1.6 Hz, CH_2CH), 50.6 (NCH_2), 71.9 (d, $^2J_{C,F}$ = 17.6 Hz, NCH), 102.1 (d, $^1J_{C,F}$ = 326.0 Hz, CBr_2F), 127.4 (Ph-CH), 129.7 (Ph-CH), 136.4 (Ph-C), 143.9 (Ph-C); δ_F (282 MHz, $CDCl_3$, $CFCl_3$):

–51.3 (1 F, d, $^3J_{H,F}$ = 10.9 Hz). Exact mass (ESI): [M+Na$^+$] calcd for $C_{12}H_{14}Br_2FNO_2SNa^+$: 439.8947/437.8968/435.8988; found: 439.8947/437.8965/435.8986.

(3*R*)-3-Fluoro-*N*-tosylpiperidine (11a)[32,33]. Isolated from the above reaction as a white solid (20 mg, 16%); mp 100 °C; $[\alpha]_D^{20}$ +12.6 (*c* 0.96 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$, TMS): 1.54–1.69 (2 H, m, CH_2 & CFHCH_2), 1.76 (1 H, m, CFHCH_2), 1.89 (1 H, m, CH_2), 2.43 (3 H, s, CH_3), 2.95 (1 H, m, NCH_2), 3.05–3.10 (2 H, m, NCH_2 & NCH_2CFH), 3.30 (1 H, ddd, $^3J_{H,F}$ = 20.1 Hz, $^2J_{H,H}$ = 11.9 Hz, $^3J_{H,H}$ = 3.2 Hz, NCH_2CFH), 4.67 (1 H, dtt, $^2J_{H,F}$ = 47.4 Hz, $^3J_{H,H}$ = 6.9 Hz, $^3J_{H,H}$ = 3.4 Hz, CFH), 7.34 (2 H, d, $^3J_{H,H}$ = 8.0 Hz, Ph-CH), 7.65 (2 H, d, $^3J_{H,H}$ = 8.3 Hz, Ph-CH); δ_C (101 MHz, $CDCl_3$): 20.9 (d, $^4J_{C,F}$ = 6.4 Hz, $CH_2CH_2CH_2$), 21.4 (CH_3), 29.1 (d, $^3J_{C,F}$ = 20.1 Hz, CH_2CFH), 45.6 (NCH_2), 49.5 (d, $^2J_{C,F}$ = 26.4 Hz, NCH_2CFH), 85.9 (d, $^1J_{C,F}$ = 176.4 Hz, CFH), 127.4 (Ph-CH), 129.6 (Ph-CH), 133.1 (Ph-C), 143.6 (Ph-C); δ_F (282 MHz, $CDCl_3$, $CFCl_3$): –183.3 (1 F, m). MS (EI-GC-inlet): *m/z* (%) 257 (38) [M$^+$], 237 (9) [M$^+$-HF], 224 (2) [$C_{11}H_{14}NO_2S^+$], 155 (38) [$C_7H_7O_2S^+$], 102 (100) [$C_5H_9NF^+$], 91 (50) [$C_7H_7^+$]. Exact mass (ESI): [M+H$^+$] calcd for $C_{12}H_{16}FNO_2SH^+$: 258.0959; found: 258.0959. Exact mass (ESI): [M+Na$^+$] calcd for $C_{12}H_{16}FNO_2SNa^+$: 280.0778; found: 280.0774.

(3*R*)-*N*-(3-Bromo-4-toluenesulfonyl)-3-fluoropiperidine (11b). Isolated from the reaction shown in Table 2, entry 4 (0.25 mmol scale; 43 mg, 51%); $[\alpha]_D^{20}$ +13.4 (*c* 1.05 in $CHCl_3$); δ (400 MHz, $CDCl_3$, TMS): 1.55–1.73 (2 H, m, CH_2), 1.74–1.99 (2 H, m, CFHCH_2), 2.48 (3 H, s, CH_3), 2.99 (1 H, m, NCH_2), 3.04–3.17 (2 H, m, NCH_2 and NCH_2CFH), 3.35 (1 H, ddd, $^3J_{H,F}$ = 20.2 Hz, $^2J_{H,H}$ = 12.0 Hz, $^3J_{H,H}$ = 3.3 Hz, NCH_2CFH), 4.68 (1 H, dtt, $^2J_{H,F}$ = 47.2, $^3J_{H,H}$ = 6.8, $^3J_{H,H}$ = 3.3 Hz, CHF), 7.39 (1 H, d, $^3J_{H,H}$ = 8.0 Hz, Ph-CH), 7.61 (1 H, dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.8 Hz, Ph-CH), 7.94 (1H, d, $^4J_{H,H}$ = 1.8 Hz, Ph-CH); δ_C (101 MHz, $CDCl_3$) 21.0 (d, $^4J_{C,F}$ = 6.3 Hz, $CH_2CH_2CH_2$), 23.1 (CH_3), 29.2 (d, $^3J_{C,F}$ = 20.1 Hz, CFHCH_2), 45.7 (NCH_2), 49.5 (d, $^2J_{C,F}$ = 26.5 Hz, NCH_2CFH), 85.8 (d, $^1J_{C,F}$ = 176.8 Hz, CFH), 125.4 (Ph-C), 126.3 (Ph-CH), 131.1 (Ph-CH), 131.2 (Ph-CH), 135.6 (Ph-C), 143.6 (Ph-C); δ_F (282 MHz, $CDCl_3$, $CFCl_3$): –183.5 (1 F, m). MS (EI-GC-inlet): *m/z* (%) 337/335 (20/21) [M$^+$], 337/335 (2/3) [M$^+$-HF], 235/233 (10/10) [$C_7H_6BrO_2S^+$], 171/169 (12/11) [$C_7H_6Br^+$], 102 (100) [$C_5H_9NF^+$], 90 (22) [$C_7H_6^+$], 89 (23) [$C_7H_5^+$], 55 (21) [$C_4H_6^+$]. Exact mass (ESI): [M+Na$^+$] calcd for $C_{12}H_{15}BrFNO_2SNa^+$: 359.9863/357.9883; found: 359.9871/357.9891.

(2*S*)-2-Fluoromethyl-*N*-tosylpyrrolidine (12). Identified by comparison of ^{19}F NMR data obtained from the reaction mixture of experiment entry 3, Table 2 with known ones;[32,33] δ_F (282 MHz, $CDCl_3$, $CFCl_3$): –225.9 (1 F, td, $^2J_{H,F}$ = 47.1 Hz, $^3J_{H,F}$ = 16.7 Hz).

Synthesis of (3*R*)-3-Fluoro-*N*-tosylpiperidine (11a) with Fluolead™ and Olah's reagent

The reaction was carried out in a 20 cm^3-Teflon™ screwed vessel. To a solution of *N*-tosyl-L-prolinol (**3**) in absolute dichloromethane (2 cm^3) Fluolead™ (250 mg, 1.0 mmol, 2.00 eq.) was added. The vessel was screwed tightly and the reaction mixture was stirred at 85 °C for 45 min. After cooling down to room temperature Olah's reagent (0.03 cm^3, 0.2 cm^3 g^{-1} of **3**, 0.22 eq.) was added *via* a polypropylene/polyethylene syringe. The mixture was stirred for 1 h at room temperature, then at 50 °C for 40 min, cooled down to room temperature, neutralized with aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 20 cm^3). The combined organic layer was washed with 15% aqueous NaOH solution, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. After column chromatography (silica gel, pentane/diethylether, 40 : 1) the product **11a** was obtained as a white solid (121 mg, 95%). As a by-product (5%, ^{19}F NMR) (2*S*)-2-fluoromethyl-*N*-tosylpyrrolidine (**12**) was found. The spectroscopic data are matching to those given above.

Synthesis of methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(phenylthio)propanoate (17)

(2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-hydroxypropanoic acid (14)[48]. According to the literature procedure L-serine (1.105 g, 10.0 mmol), sodium carbonate (1.090 g, 10.0 mmol) and *N*-ethoxycarbonylphthalimide (2.190 g, 10.0 mmol) was reacted in water (8 cm^3) and the product was obtained as a white solid (2.115 g, 90%); mp 152 °C (with decomposition); $[\alpha]_D^{20}$ –8.77 (*c* 1.00 in $CHCl_3$); δ_H (300 MHz, D_2O): 1.17 (1 H, t, $^3J_{H,H}$ = 7.1 Hz, CH_2OH), 4.02 (1 H, m, CH_2OH), 4.11 (1 H, m, CH_2OH), 5.00 (1 H, m, NCH), 7.71–7.84 (4 H, m, Ph-CH); δ_C (75 MHz, D_2O): 54.0 (NCH), 58.8 (CH_2OH), 123.4 (Ph-CH), 130.8 (Ph-C), 135.8 (Ph-CH), 169.6 (NCO), 171.5 (COOH). Exact mass (ESI): [M+Na$^+$] calcd for $C_{11}H_9NO_5Na^+$: 258.0373; found: 258.0360. Exact mass (ESI): [M-H$^-$] calcd for $C_{11}H_8NO_5^-$: 234.0408; found: 234.0406.

Methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-hydroxypropanoate (15). (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-hydroxypropanoic acid (**14**) (2.352 g, 10.0 mmol) was dissolved in methanol (20 cm^3). Concentrated sulfuric acid (1.07 cm^3, 1.960 g, 2.0 mmol, 0.2 eq.) was added and the reaction mixture was stirred at 40 °C for 2 days. Quenching with ice water (50 cm^3), extraction with diethyl ether (3 × 50 cm^3), washing of the combined organic layer with saturated $NaHCO_3$ and water (2 × 50 cm^3), drying over anhydrous $MgSO_4$ and removing of the solvent under reduced pressure led to the product **15** as a colorless oil (2.240 g, 90%); $[\alpha]_D^{20}$ –10.3 (*c* 1.19 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$, TMS): 1.20 (1 H, t, $^3J_{H,H}$ = 7.1 Hz, CH_2OH), 3.76 (3 H, s, CH_3), 3.85–3.92 (1 H, m, CH_2OH) 4.19–4.25 (1 H, m, CH_2OH), 5.04 (1 H, dd, $^3J_{H,H}$ = 6.1 Hz, $^3J_{H,H}$ = 5.0 Hz, NCH), 7.75 (2 H, dd, $^3J_{H,H}$ = 5.6 Hz, $^4J_{H,H}$ = 3.0 Hz, Ph-CH), 7.86 (2 H, dd, $^3J_{H,H}$ = 5.4 Hz, $^4J_{H,H}$ = 3.1 Hz, Ph-CH); δ_C (75 MHz, $CDCl_3$): 52.9 (OCH_3), 54.7 (NCH), 61.0 (CH_2OH), 123.7 (Ph-CH), 131.6 (Ph-C), 134.4 (Ph-CH), 168.0 (NCO), 168.4 (*C*OOCH$_3$). Exact mass (ESI): [M+H$^+$] calcd for $C_{12}H_{11}NO_5H^+$: 250.0710; found: 250.0708. Exact mass (ESI): [M+Na$^+$] calcd for $C_{12}H_{11}NO_5Na^+$: 272.0529; found: 272.0528. Exact mass (ESI): [M-H$^-$] calcd for $C_{12}H_{10}NO_5^-$: 248.0564; found: 248.0546.

Methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(phenylthio)-propanoate (17). According to the literature procedure[39] to a solution of compound **15** (125 mg, 0.5 mmol) in abs. *N*,*N*-dimethylformamide tributylphospine (0.19 cm^3, 0.75 mmol, 1.5 eq.) and diphenyldisulfide (164 mg, 0.75 mmol, 1.5 eq.) were added. After stirring for 1 h at room temperature the reaction mixture was diluted with diethyl ether (10 cm^3), washed with saturated $NaHCO_3$ solution, water and brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. After column chromatography (neutral alumnia, cyclohexane/ethyl

acetate, 20 : 1) the product **17** was obtained as a colorless oil (118 mg, 69%); $[\alpha]_D^{20}$ –0.88 (*c* 1.03 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$, TMS): 3.69–3.92 (2 H, m, PhSCH_2), 3.73 (3 H, s, CH_3), 5.01 (1 H, dd, $^3J_{H,H}$ = 11.0 Hz,$^3J_{H,H}$ = 4.2 Hz, NCH), 7.06 (1 H, m, Ph-CH), 7.16 (2 H, m, Ph-CH), 7.35 (2 H, m, Ph-CH), 7.72 (2 H, m, Ph-CH), 7.79 (2 H, dd, $^3J_{H,H}$ = 5.7 Hz, $^4J_{H,H}$ = 3.0 Hz, Ph-CH); δ_C (75 MHz, $CDCl_3$): 33.5 (PhS*C*H$_2$), 52.0 (OCH_3), 52.9 (NCH), 123.4 (Ph-CH), 127.0 (Ph-CH), 128.9 (Ph-CH), 131.3 (Ph-CH), 131.5 (Ph-C), 133.6 (Ph-C), 134.0 (Ph-CH), 167.2 (NCO), 168.4 (*C*OOCH$_3$). Exact mass (ESI): [M+Na$^+$] calcd for $C_{18}H_{15}NO_4SNa^+$: 364.0614; found: 364.0616.

Oxidative desulfurization–difluorination of methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(phenylthio)propanoate (17)

According to above general procedure for the oxidative desulfurization–fluorination, methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(phenylthio)-propanoate (**17**) (86 mg, 0.25 mmol) in dry dichloromethane (5 cm^3) was reacted with Olah's reagent (0.35 cm^3, 1.5 mmol, 6 eq.) and DBH (215 mg, 0.75 mmol, 3 eq.) while stirring for 30 min at 0 °C and at room temperature over night. Then the reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with dichloromethane (3 × 10 cm^3). The combined organic layer was washed with 1 N HCl, 5% aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. After column chromatography (neutral alumina, cyclohexane/ethyl acetate, 20 : 1) a lightly yellow solid was obtained. Recrystallization from pentane–diethyl ether gave colorless crystals of compound **19**, which were subjected to X-ray crystallography.

Methyl (2*S*)-2-(1,3-dioxoisoindolin-2-yl)-3,3-difluoropropionate (18). The formed minor component **18** could only be detected by ESI mass spectrometry and ^{19}F NMR spectroscopy. δ_F (282 MHz, $CDCl_3$, $CFCl_3$): –118.0 (2 F, ddd, $^2J_{F,F}$ = 5.5 Hz, $^2J_{H,F}$ = 63.0 Hz, $^3J_{H,F}$ = 21.3 Hz). Exact mass (ESI): [M+Na$^+$] calcd for $C_{12}H_9F_2NO_4Na^+$: 292.0392; found: 292.0380.

Methyl 2,2-dibromo-2-(1,1-difluoro-3–oxoisoindolin-2-yl)acetate (19). (21 mg, 21%); mp 125–126 °C; δ_H (500 MHz, $CDCl_3$, TMS): 3.96 (3 H, s, CH_3), 7.73 (1 H, m, Ph-CH), 7.78–7.83 (2 H, m, Ph-CH), 7.85–7.89 (1 H, d, $^3J_{H,H}$ = 7.6 Hz, Ph-CH); δ_C (126 MHz, $CDCl_3$): 51.8 (t, $^3J_{C,F}$ = 1.2 Hz, Br_2NCCO), 55.4 (CH_3), 120.4 (t, $^1J_{C,F}$ = 256.8 Hz, CF_2N), 122.5 (Ph-CH), 124.5 (Ph-CH), 127.6 (t, $^3J_{C,F}$ = 2.3 Hz, Ph-C), 132.9 (Ph-C), 135.2 (Ph-CH), 138.0 (t, $^2J_{C,F}$ = 26.1 Hz, Ph-C), 163.3 (*C*OOCH$_3$), 163.6 (NCO); δ_F (470 MHz, $CDCl_3$, $CFCl_3$): –87.0 (2 F, s). MS (EI-GC-inlet): *m*/*z* (%) 401/399/397 (<0.1/<0.1/<0.1) [M$^+$], 370/368/366 (1/2/1) [M$^+$-CH_3O], 342/340/338 (4/9/4) [M$^+$-$C_2H_3O_2$], 320/318 (100/98) [M$^+$-Br], 235/233 (66/68), 180 (38) [$C_{11}H_7Br_2F_2NO_3^+$], 154 (72), 152 (47) [$C_8H_4F_2N^+$], 126 (89) [$C_4H_7F_2^+$], 125 (66). Exact mass (ESI): [M+Na$^+$] calcd for $C_{11}H_7Br_2F_2NO_3Na^+$: 423.8612/421.8633/419.8653; found: 423.8615/421.8635/419.8659.

Crystallographic data

Crystal structure analysis of compound **19**: $C_{11}H_7Br_2F_2NO_3$, *M* = 399.00, colorless crystal 0.40 × 0.10 × 0.01 mm, *a* = 13.5963(9), *b* = 7.1431(5), *c* = 13.1021(9) Å, *β* = 94.214(3)°, *V* = 1269.03(15) Å^3, ρ_c = 2.088 g cm^{-3}, μ = 8.408 mm^{-1}, empirical absorption correction (0.134 SYMBOL 163 \f "Symbol" *T* SYMBOL 163 \f "Symbol" 0.921), *Z* = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, *T* = 223(2) K, ω and φ scans, 7604 reflections collected (SYMBOL 177 \f "Symbol"*h*, SYMBOL 177 \f "Symbol"*k*, SYMBOL 177 \f "Symbol"*l*), [(sin*θ*)/*λ*] = 0.60 Å^{-1}, 2197 independent (R_{int} = 0.050) and 2007 observed reflections [*I* SYMBOL 179 \f "Symbol" 2 SYMBOL 115 \f "Symbol"(*I*)], 173 refined parameters, *R* = 0.047, wR^2 = 0.147, max. (min.) residual electron density 0.93 (–0.94) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms. *R*-values are given for the observed reflections, wR^2-values for all reflections.

Data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN,[49] absorption correction Denzo,[50] structure solution SHELXS-97,[51] structure refinement SHELXL-97,[52] graphics SCHAKAL (E. Keller, Univ. Freiburg, 1997).

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