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Asymmetric Synthesis of Merck's Potent hNK$_1$ Antagonist and Its Stereoisomers via Tandem Acylation/[3,3]-Rearrangement of 1,2-Oxazine-*N*-oxides

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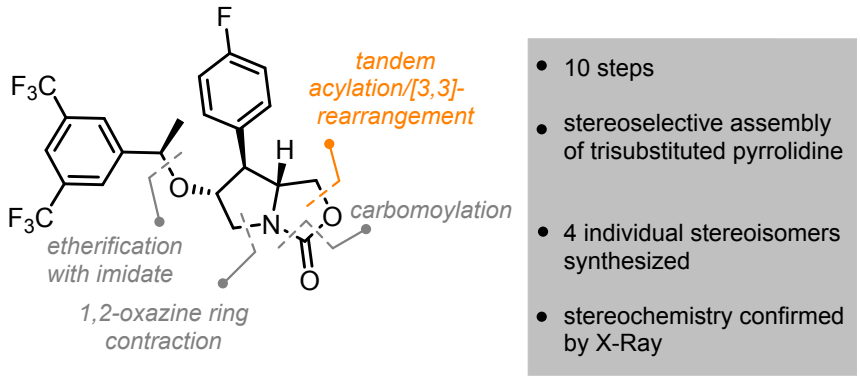


Merck's potent hNK$_1$ antagonist

Abstract: An asymmetric total synthesis of Merck's hNK$_1$ antagonist and three of its stereoisomers was accomplished in 10 steps. The synthesis involves a stereoselective assembly of 1,2-oxazine-*N*-oxide by the [4+2]-cycloaddition, site-selective C–H oxygenation using a novel tandem acylation/[3,3]-rearrangement process and the reductive 1,2-oxazine ring contraction into a pyrrolidine ring as key stages. Using this strategy, the fused pyrrolidine subunit was constructed with exceptionally high regio- and stereoselectivities. The approach

described here can be used to access enantiopure 3,4-disubstituted prolinols, which are frequently found in pharmaceutically relevant molecules and organocatalysts.

Introduction and background

Neurokinins are peptides that modulate a wide variety of processes in human physiology through the neurokinin G-protein-coupled receptors (GPCRs) involved in numerous pathological processes.[1] Human neurokinin 1 (hNK_1) receptor antagonists have gained considerable interest as inhibitors of emesis associated with cancer chemotherapy.[2] Aprepitant (Emend®) developed by Merck was the first selective hNK_1 antagonist used as a treatment for chemotherapy-induced and postoperative nausea and vomiting.[3] Later, other structurally related hNK_1 antagonists such as Fosaprepitant (Ivemend®),[3c,4] Rolapitant (Varubi®)[5] and Netupitant (Akynzeo®)[6] with improved performance were approved by FDA for the use as antiemetic drugs. Further research revealed the potential of hNK_1 antagonists for treatment of various CNS disorders owing to their ability to penetrate the blood-brain barrier.[7]

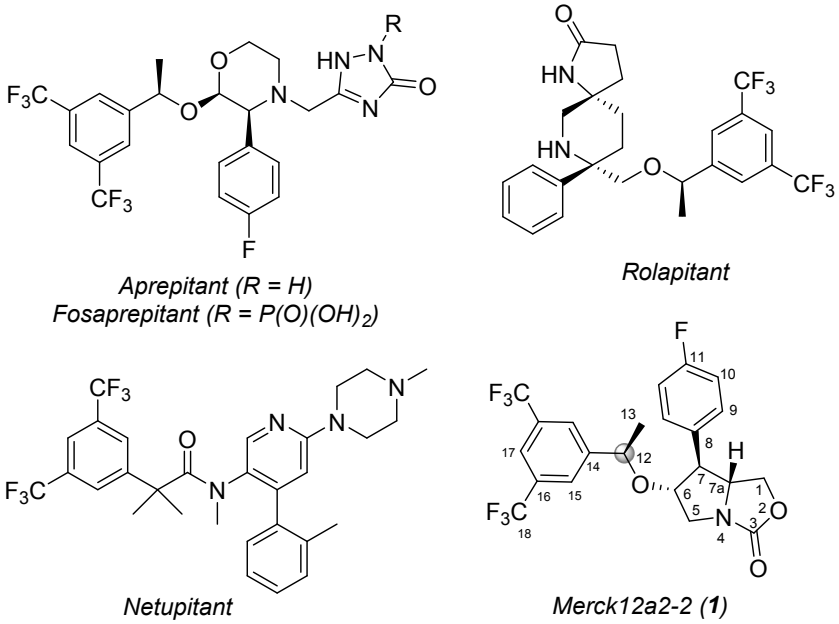
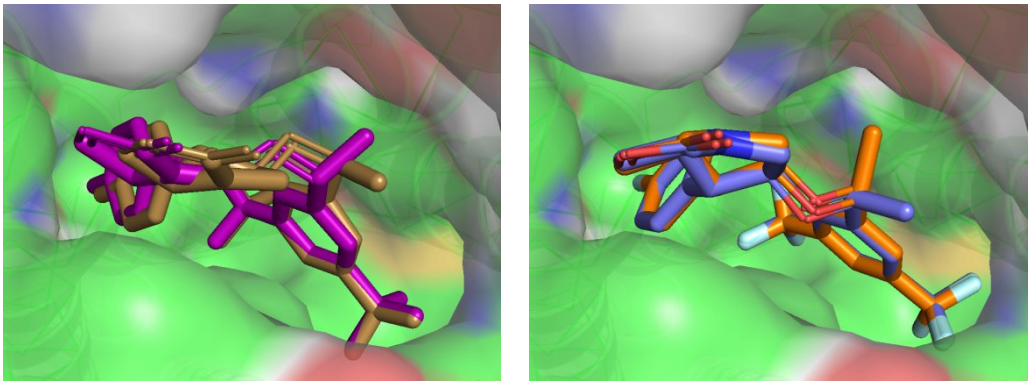


Figure 1. Aprepitant and its analogs

In the course of Merck's studies aimed at finding efficient analogs of Aprepitant,[8] a fused pyrrolooxazolidinone Merck12-a2-2 (**1**) was identified as a lead compound among a series of bicyclic aryl-substituted pyrrolidine derivatives (Figure 1).[8a] However, the synthesis of this molecule developed by Merck gave rise to low regio- and diastereoselectivities of reactions used to assemble the 3,4-disubstituted prolinol motif.[8a]

Among sixteen possible stereoisomers of compound **1** only the one, which is shown in Figure 1, was prepared by Merck.[8a] Given the spatial structure of antagonist **1** with a large Fsp^3 index (four stereogenic centers, two saturated heterocycles), one can expect that the binding of its stereoisomers to hNK_1 receptor may differ. Molecular docking of compound **1** or its C-12 epimer **1'** using the recently reported[9] crystallographic structure of hNK_1 receptor demonstrate that aryl rings serve as anchoring groups, while the spatial orientation of the C-13 methyl is different (Figure 2, A).[10] Same picture is observed for enantiomers of **1** and **1'** (Figure 2, B). This is in line with a known fact that the hNK_1 binding activity of Aprepitant analogs depends on the absolute configuration of the bis(trifluoromethyl)phenylethoxy unit.[8a]



(A) (B)

Figure 2. Molecular docking of **1** and its stereoisomers into the binding site of hNK_1 receptor (PDB: 6HLO): view on the C-13 methyl group. (A) Superimposition of stereoisomers (6*R*,7*S*,7a*R*,12*R*)-**1** (magenta) and (6*R*,7*S*,7a*R*,12*S*)-**1'** (sand). (B) Superimposition of stereoisomers (6*S*,7*R*,7a*S*,12*S*)-**1** (blue) and (6*S*,7*R*,7a*S*,12*R*)-**1'** (orange)'

The stereochemistry of hNK_1 antagonist **1** postulated in Merck's paper[8a] seems to be ambiguous, since no confirmation of the absolute configuration of the stereocenter C-12 was provided.[11] Hence, the compound synthesized and studied by Merck could be the C-12 epimer of **1** (compound **1'**), which is expected to be less potent. Moreover, no spectroscopic characterization data for compound **1** was given.[8a] This leaves the question of stereochemistry of compound **1** and structure-activity relationship for its stereoisomers to be clarified. For the reasons outlined above, a convenient asymmetric synthesis of Merck12-a2-2 **1**, which allows for the preparation of its stereoisomers and establishment of their absolute stereochemistry, is needed.

In continuation of our studies towards total synthesis of bioactive pyrrolidine derivatives,[12] we describe herein an asymmetric synthesis and full characterization of individual Merck12-a2-2 (**1**), its C-12 epimer (**1'**) and their enantiomers. The strategy disclosed in this paper provides a general stereoselective access to polysubstituted prolinols, which are frequently found in pharmaceutically relevant molecules.

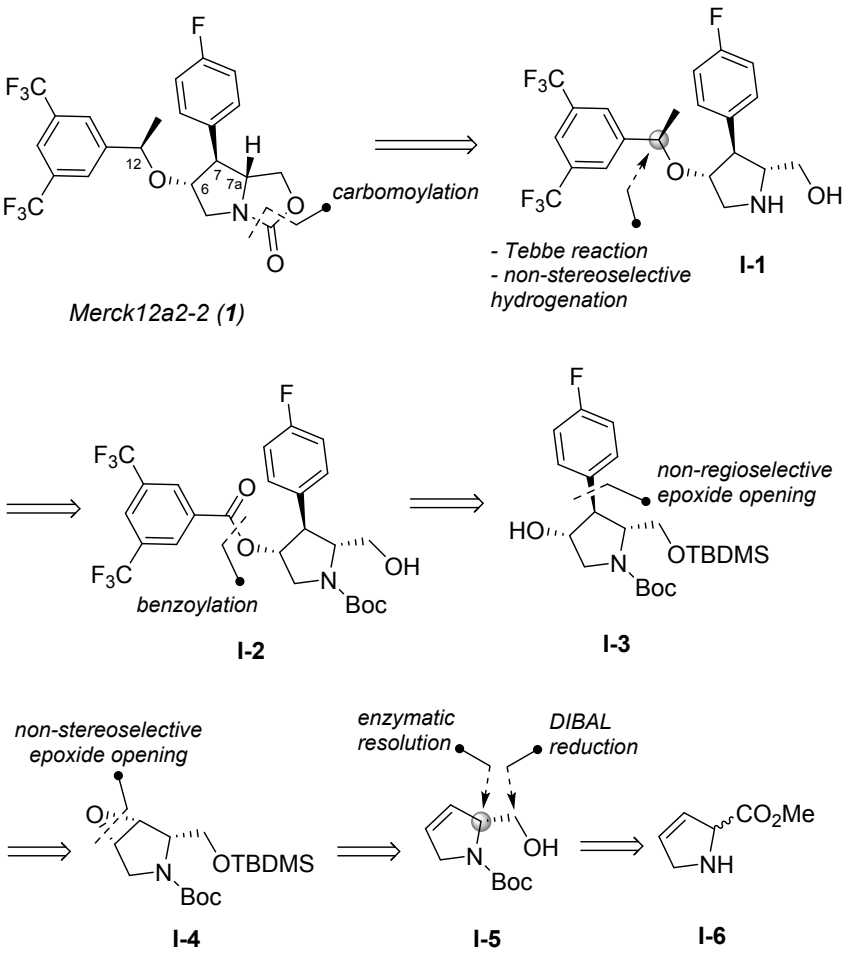
Results and Discussion

The synthesis of Merck12-a2-2 (**1**) is challenging due to the presence of a fused pyrrolidine skeleton possessing three contiguous stereogenic centers with a pre-defined configuration. The construction of a *sec-sec* ether connection between C-6 and C-12 atoms is also difficult since bis(trifluoromethyl)phenylethyl halides and sulfonates exhibit very poor reactivity in S_N reactions.[13]

The synthetic strategy towards compound **1** used by Merck is depicted in Scheme 1.[8a] According to this strategy, the final stage was the construction of the oxazolidinone ring by carbomoylation of prolinol intermediate **I-1**. The *sec-sec* ether unit was formed from the corresponding benzoyl ester **I-2** by Tebbe reaction and subsequent hydrogenation of the double C,C-bond, which was not stereoselective. The introduction of aryl group in the pyrrolidine ring

(**I-3**) was accomplished by the addition of 4-fluorophenyl magnesium bromide to the epoxide **I-4**. However, the epoxide ring opening was not regioselective and produced 3- and 4-aryl substituted pyrrolidines in nearly equal amounts. The epoxide **I-4** was prepared by non-stereoselective epoxidation of (*R*)-3,4-dehydroprolinol **I-5** (d.r. 2 : 1), which was obtained from the racemic 3,4-dehydroproline **I-6** using an enzymatic resolution process and subsequent DIBAL reduction of the ester group. Thus, this 13-steps synthesis of hNK_1 antagonist **1** suffered from low regio- and stereoselectivity in the construction of the trisubstituted pyrrolidine ring. For none of these intermediates (as well as for the final compound) the X-Ray analysis was performed to confirm the stereochemistry.

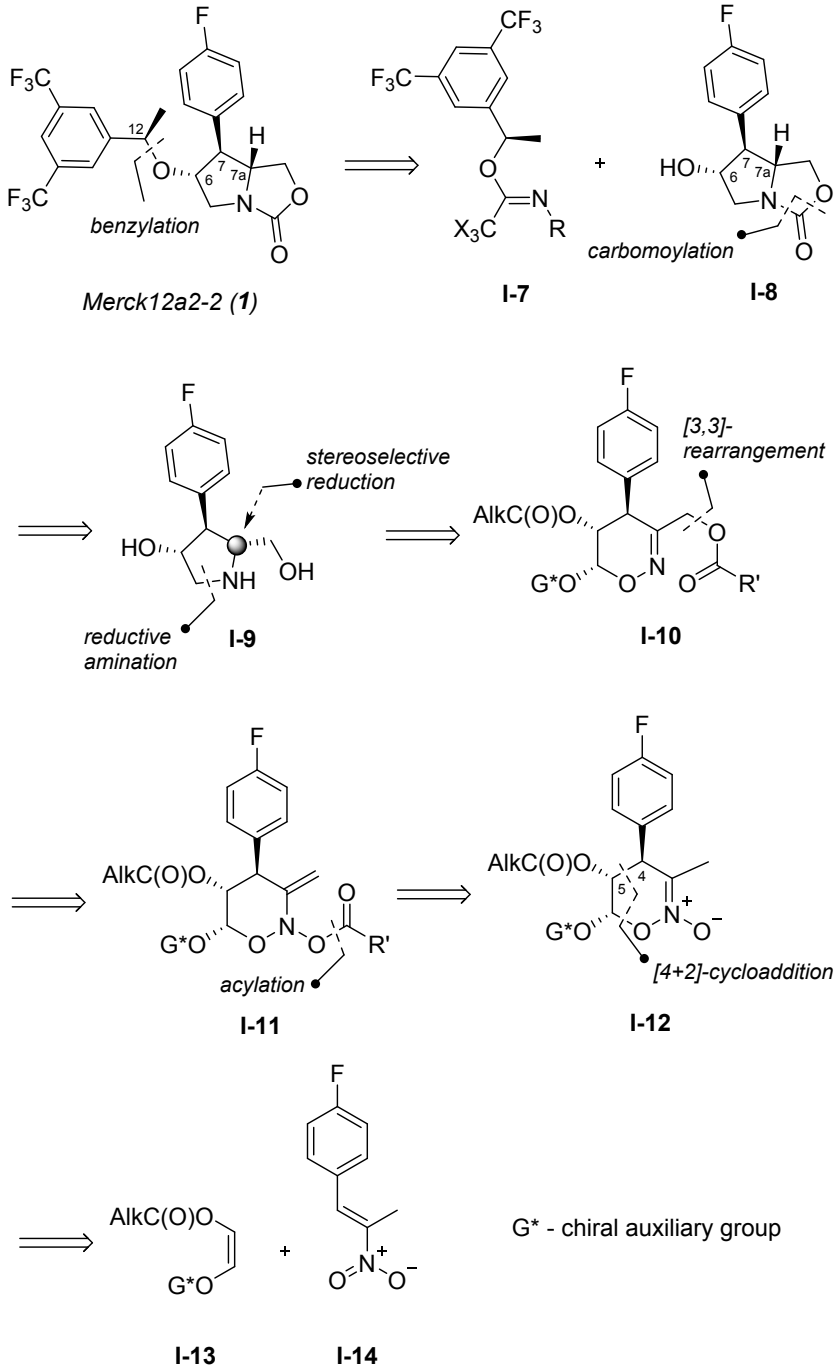
Scheme 1. Merck's strategy to hNK_1 antagonist **1**



In our synthesis of Merck12-a2-2 (**1**), a completely different strategy to construct the trisubstituted pyrrolidine motif was undertaken in order to ensure complete regio- and stereocontrol. Moreover, in contrast to Merck's synthesis we planned to introduce bis(trifluoromethyl)phenylethyl group at the last stage of the synthesis by using acid-mediated S_N reactions between bis(trifluoromethyl)phenylethyl imidates **I-7** and secondary alcohol **I-8** (Scheme 2).

According to our strategy, the enantiopure 3-aryl-substituted prolinol **I-9** could be accessed by the reductive contraction of the 1,2-oxazine ring having an alkoxy-group at the C-6 position (Scheme 2, *vide infra*).[14] To synthesize the required 1,2-oxazine **I-10**, we planned to use the spontaneous [3,3]-sigmatropic rearrangement of *N*-acyloxy,*N*-oxyenamines of type **I-11**, which could be generated *in situ* by the acylation of 1,2-oxazine-*N*-oxide **I-12**. This straightforward and very mild CH-oxygenation of non-aromatic *N*-oxides was recently developed by us,[15] and here we intended to test its application in asymmetric total synthesis for the first time. The corresponding 1,2-oxazine-*N*-oxide **I-12** could be assembled by an inverse electron demand [4+2]-cycloaddition of a simple nitroalkene **I-14** and a dienophile **I-13** bearing a chiral auxiliary group. Given the known high *exo*-selectivity in this type of cycloaddition reactions,[16] we anticipated to establish the required 4,5-*trans*-disposition of the aryl and the acyloxy-group in the 1,2-oxazine ring. Moreover, [4+2] reactions of nitroalkenes with l-(acyloxy)-2-alkoxyethenes of type **I-13** proceed in a regioselective fashion affording 1,2-oxazine-*N*-oxides with the acyloxy-group at the C-5 position as reported by Denmark et al.[16]

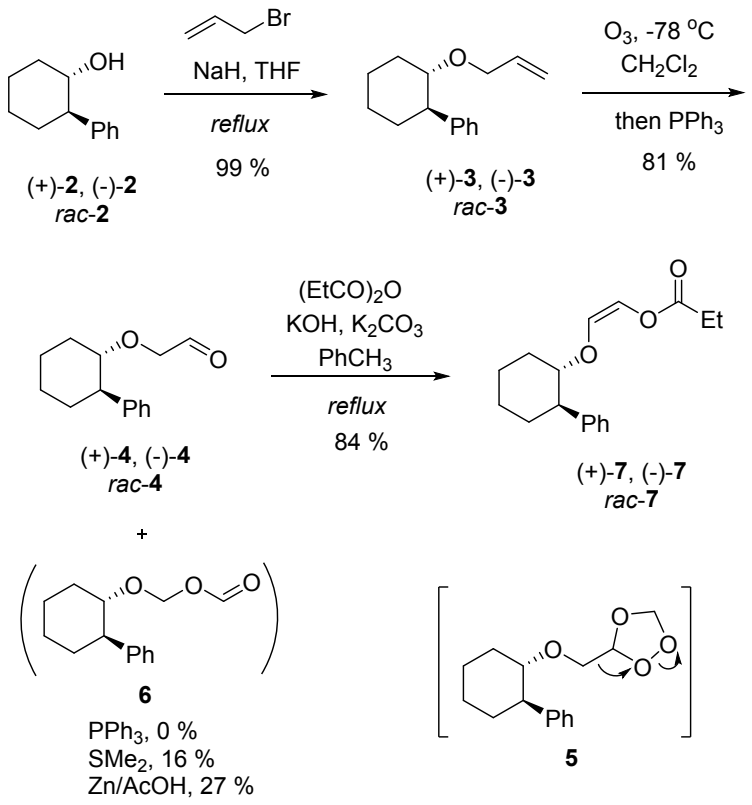
Scheme 2. Proposed strategy to Merck12-a2-2 (**1**)



We started with the preparation of the dienophile **I-13** bearing a chiral alkoxy-group (Scheme 3). Based on the previous studies,[12a,17] Whitesell's auxiliary (*trans*-2-phenylcyclohexyl ether) was chosen as G* group, because it is known to induce high levels of stereocontrol in [4+2]-cycloaddition reactions. Commercially available (+)- and (–)-*trans*-2-phenylcyclohexanols **2** were transformed into allyl ethers **3**, which were then subjected to ozonolysis to afford the

corresponding aldehydes **4**. At this stage, the procedure for the reductive cleavage of trioxolane **5** was found to be crucial. With Zn/AcOH, only 34 % yield of aldehyde **4** was obtained along with 27 % of unexpected formate **6**, which likely results from the peroxide rearrangement in trioxolane **5**. Interestingly, in the reduction with SMe_2, formate was also generated, yet in a smaller amount. Fortunately, when PPh_3 was used as a reducing agent, only the desired aldehyde **4** was obtained in 70 % yield. Acylation of aldehydes **4** with propionic anhydride in the presence of K_2CO_3/KOH afforded alkenes **7** almost solely as *Z*-isomers.

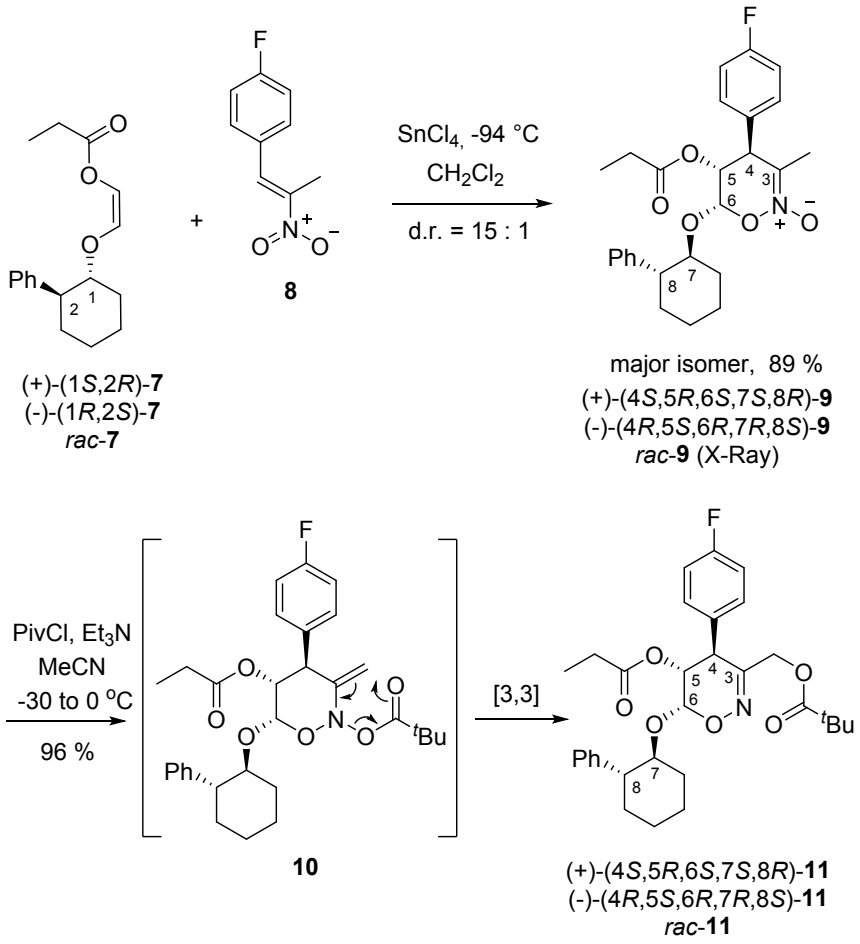
Scheme 3. Steps (1) – (3): synthesis of dienophiles **7**



With two enantiomeric dienophiles (+)-**7** and (–)-**7** in hand, their [4+2]-cycloaddition with nitroalkene to give nitronates **9** was investigated (Scheme 4). Denmark et al reported,[18] that l-acyloxy-2-((2-phenylcyclohexyl)oxy)ethenes of type **7** show poor π-facial stereoselectivity in MAPh-promoted [4+2]-cycloaddition with nitroalkenes. In our case, however, the $SnCl_4$-promoted reaction turned to be highly stereoselective and afforded only two of four possible

stereoisomers of the 1,2-oxazine-*N*-oxide **9** in 10 : 1 ratio. The major isomer could be easily separated by column chromatography. NMR studies revealed that the major isomer has 4,5-*trans*-stereochemistry and originates from the *exo*-approach of dienophile **7** to nitroalkenes **9**. Thus, exceptionally high *exo*- and π-facial selectivity were observed in the formation of nitronate **9** from dienophile **7**. Using this method, both enantiomers (+)-**9** and (−)-**9** were prepared on up to three grams scale with ee > 99 % and d.r. 30 : 1 (chiral HPLC) after column chromatography.

Scheme 4. Steps (4) – (5): assembly 1,2-oxazine-*N*-oxaides **9** and their functionalization



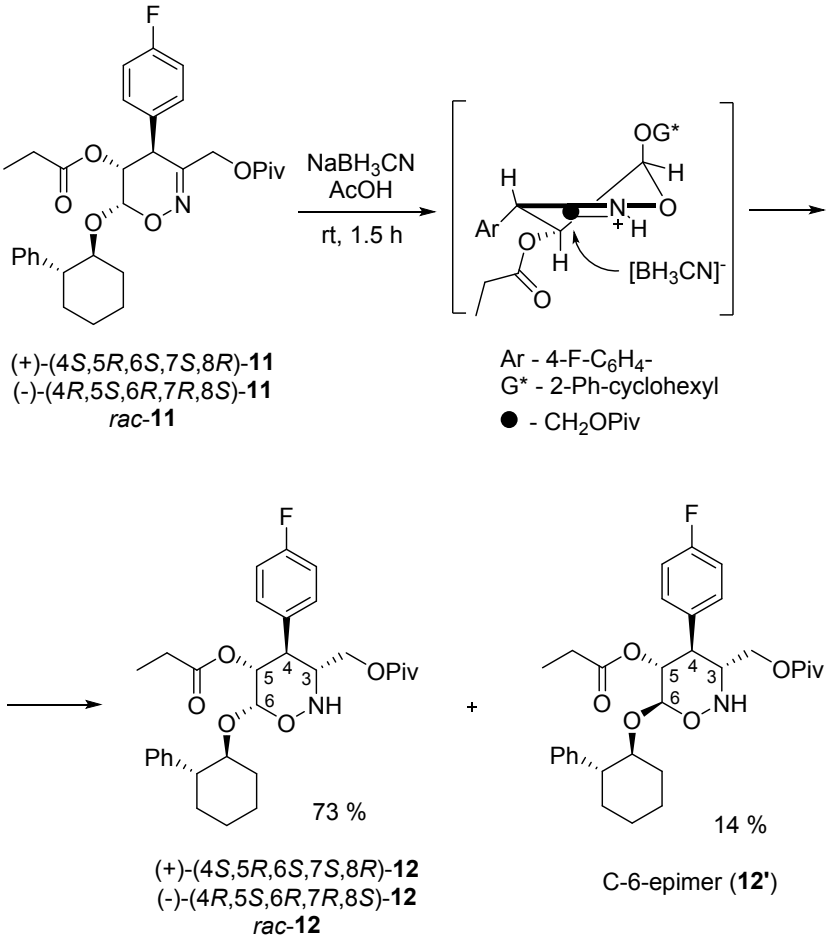
Although two stereogenic centers of the target molecule were now set, their absolute stereochemistry could not be determined from NMR data. We were not able to obtain crystals for the X-Ray analysis from the enantiopure samples of *N*-oxide **9**. Fortunately, we succeeded in getting X-Ray data for the racemic *N*-oxide *rac*-**9**, which was specially prepared from the

racemic *trans*-2-phenylcyclohexanol *rac*-**2** using the same synthetic sequence. Given the known configuration of the chiral auxiliary, the absolute stereochemistry of enantiomeric 1,2-oxazine-*N*-oxides (+)-**9** and (–)-**9** could be unambiguously deduced from the relative configuration of stereocenters in *rac*-**9** determined by X-Ray.

Each of enantiomeric 1,2-oxazine-*N*-oxides (+)-**9** and (–)-**9** was subjected to acylation with pivaloyl chloride/Et_3N under conditions reported by us previously (Scheme 4).[14] We were pleased to find, that the desired 3-pivaloyloxymethyl-1,2-oxazines (+)-**11** and (–)-**11** originating from the [3,3]-rearrangement of transient *N*-acyloxyenamines **10** were obtained in 96 % yield under very mild conditions and without any epimerization of the sensitive acetal moiety at C-6. Importantly, this protocol proved to be highly site-selective, since oxygenation of the *endo*-cyclic C-4 carbon was not observed.

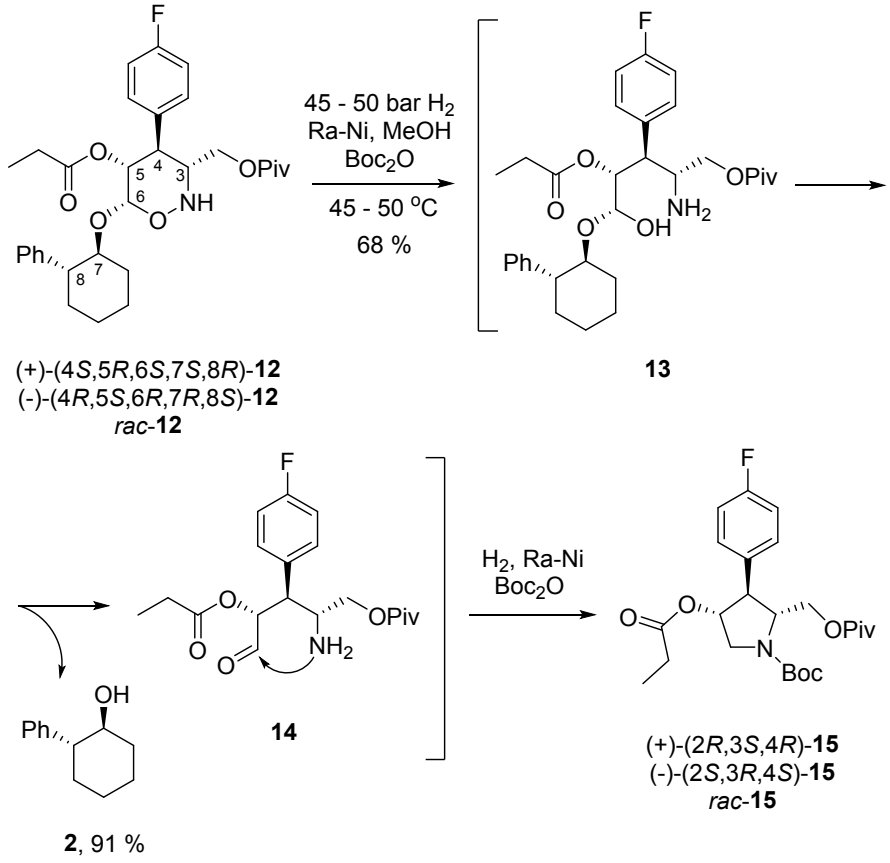
On the next stage, reductive ring contraction of 1,2-oxazine to the pyrrolidine ring had to be performed according to our synthetic plan. However, direct catalytic hydrogenation of the oxime unit in 1,2-oxazines is known to be non-chemoselective and non-stereoselective attributed to the formation of highly reactive C=NH imines as intermediates.[19] For this reason, hydride reduction of the C=N bond with $NaBH_3CN$ in acetic acid was initially performed (Scheme 5). Fortunately, the reduction of **11** was stereospecific and afforded solely the required 3,4-*trans*-isomer of fully saturated 1,2-oxazine **12**. The *trans*-disposition of hydrogens H-3 and H-4 was deduced from the 1,2-diaxial spin-spin coupling constant ($J_{H\text{-}3/H\text{-}4}$ = 10.3 Hz) and the presence of 1,3-diaxial interaction between hydrogens H-3 and H-5 in the 2D NOESY spectra. Thus, the last stereogenic center of the bicyclic moiety of target Merck12-a2-2 was correctly installed at this stage. This stereochemical result is in line with the axial addition of the hydride to the most stable twist-like conformation of protonated 1,2-oxazine **11** leading to the chair-like conformation of product **12**. It is noteworthy, that we observed small amounts of the C-6 epimer **12'**, which, however, could be used in the next step equally to the major isomer **12**.

Scheme 5. Step (6): hydride reduction of the oxime C=N bond in 1,2-oxazines **11**



Hydrogenation of 1,2-oxazines (+)-**12** and (–)-**12** over Raney nickel led to the formation of the protected prolinol derivatives, which were formed via tandem hydrogenolysis of the N–O bond, fragmentation of the hemiacetal moiety in **13** to give **14** and subsequent intramolecular reductive amination in the intermediate **14** (Scheme 6).[14] At this stage, the chiral auxiliary alcohol **2** could be recovered (91 %) for further reuse. At least 1 g quantity of protected prolinols (+)-**15** and (–)-**15** could be prepared according to this method. Thus, we succeeded in preparing the key unit of target Merck12-a2-2 (pyrrolidine ring with three contiguous stereogenic centers) in a regio- and stereoselective manner on gram scale.

Scheme 6. Step (7): reductive contraction of 1,2-oxazine ring in **12**



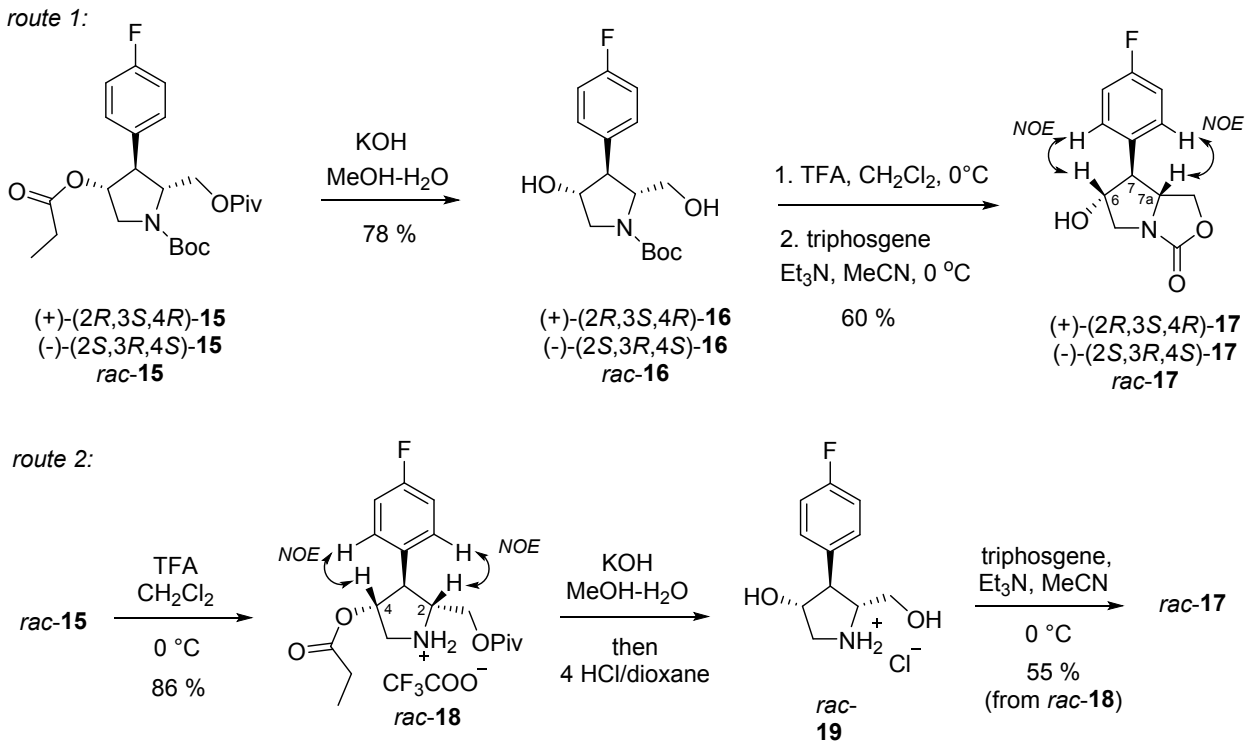
Next, the construction of oxazolidinone ring to complete the fused bicyclic framework of Merck12-a2-2 was performed. To do so, careful saponification of ester groups in **15** with 1 M KOH in aqueous methanol to give Boc-protected diols **16** was initially carried out (Scheme 7, route 1). Diols **16** were treated with TFA to remove Boc-group, and the resulting deprotected prolinols were reacted without isolation with triphosgene and Et_3N to give the desired saturated pyrrolooxazolidinones (+)-**17** and (–)-**17** in an acceptable yield.

Alternatively, the synthesis of fused pyrrolidines **17** from prolinols **15** could be accomplished using an inverted sequence of deprotection operations as demonstrated on the racemic substrate (Scheme 7, route 2). Boc-group was removed with TFA to give salt *rac*-**18** followed by hydrolysis of esters with KOH and acidification to give hydrochloride *rac*-**19**. However, separation of highly polar hydrochloride *rac*-**19** from residual inorganic salts and carboxylic acids was problematic, while the presence of impurities dramatically decreased the yield in the

subsequent reaction with triphosgene. Nevertheless, treatment of purified hydrochloride *rac*-**19** with triphosgene and Et_3N afforded the desired pyrrolooxazolidinone *rac*-**17** in an acceptable yield.

At this point, the relative configuration of stereocenters in pyrrolidine **18** and pyrrolooxazolidinone **17** was secured by 2D NMR including COSY, HSQC, HMBC and NOESY (see Experimental section and Supporting information). In the 2D NOESY spectra of product **17**, characteristic correlations between the aryl ring and hydrogens H-7a and H-6 were observed, which confirm the proposed stereochemistry of the bicyclic motif (Scheme 7). Similar correlations were found in the 2D NOESY spectra of pyrrolidine **18**.

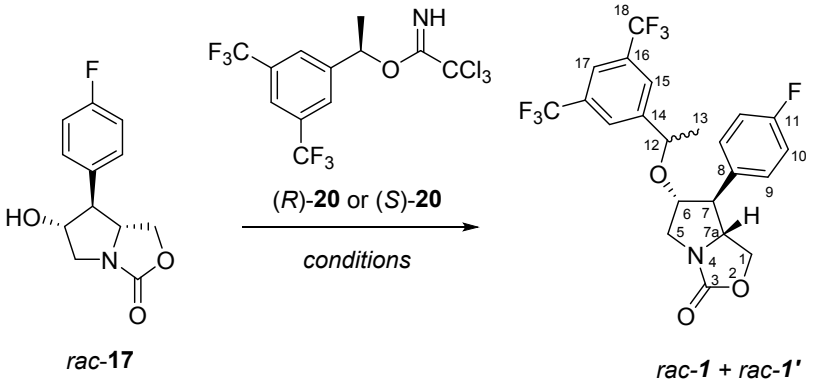
Scheme 7. Steps (8) – (9): construction of fused pyrrolidine subunit of Merck12-a2-2



To complete the synthesis of target hNK_1 antagonist **1**, bis(trifluoromethyl)phenylethyl ether moiety had to be installed at the free hydroxyl group in the bicyclic intermediate **17**. Following the report by Kuethe et al,[13] we attempted to use bis(trifluoromethyl)phenylethanol trichloroimidate **20** as an electrophile for the construction of the *sec-sec* ether unit under

catalysis with strong protic acids. Model reaction of the racemic secondary alcohol *rac*-**17** with the imidate (*R*)-**20** in the presence of HBF_4•Et_2O did give the desired ether **1** as a mixture of two diastereomers with a combined yield of only 15 % (Scheme 8). Variation of solvent, temperature, the nature and the amount of protic acid did not result in any significant increase of the yield (see Supporting information for details). Fortunately, we found that the use of a stoichiometric amount of TMSOTf instead of a protic acid resulted in the formation of the desired ether in a better yield (34 %) as a 1.4 : 1 mixture of C-12 epimers along with some amount of TMS-ether of the initial pyrrolooxazolidinone **17**. Same stereochemical result was observed with the enantiomeric imidate (*S*)-**20**. Chiral HPLC analysis revealed that both epimers were racemates demonstrating that the etherification reaction proceeds through an S_N1-like mechanism.

Scheme 8. Benzylation of *rac*-**17** with trichloroimidates **20**

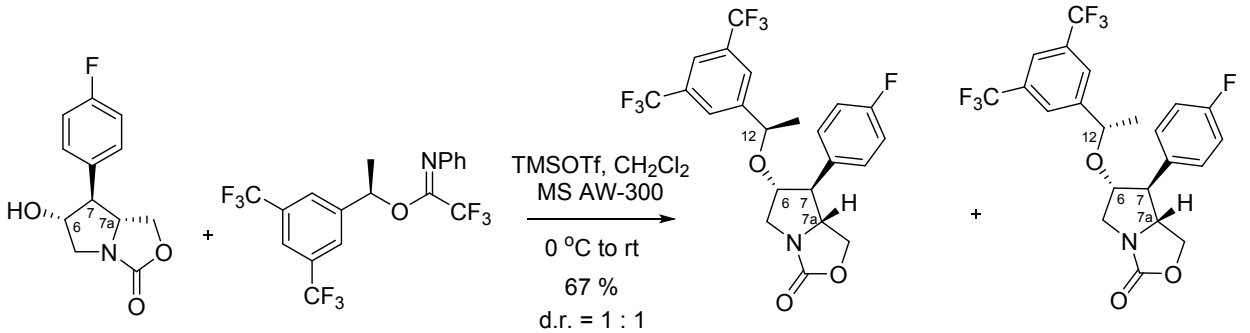


Conditions	*Yield (d.r. rac-**1**/rac-**1'**)*
HBF_4•Et_2O (0.15 eq.), DCM/cyclohexane, 0 °C, 24 h	15 % (1 : 1)
TMSOTf (1.25 eq.), CH_2Cl_2, 0 °C, 24 h	34 % (1.4 : 1)

From recent total synthesis of some complex carbohydrates,[20] we learned that 2,2,2-trifluoro-*N*-phenylacetimidates are highly efficient electrophiles in the formation of glycosidic linkages.[21] To test this approach for the construction of *sec-sec* bis(trifluoromethyl)phenylethyl ether motif, a new 2,2,2-trifluoro-*N*-phenylacetimidate (*R*)-**21** was prepared and tested in the TMSOTf-

promoted reaction with alcohols **17** (Scheme 9). The desired *sec*-*sec* ether was obtained in 67 % yield as a nearly stoichiometric mixture of C-12 epimers. The isomers could be easily separated by column chromatography on silica gel (slow moving isomer *rac*-**1** and fast moving *rac*-**1'**). Application of this procedure separately to (+)-**17** and (–)-**17** delivered target Merck12-a2-2 (**1**) and three of its stereoisomers individually. The enantiomeric purity of all obtained samples was > 96 % ee as determined by chiral HPLC analysis.

Scheme 9. Step (10): Introduction of bis(trifluoromethyl)phenylethyl group into pyrrolooxazolidinones (+)-**17** and (–)-**17**



(6*R*,7*S*,7a*R*)-**17** (*R*)-**21** (6*R*,7*S*,7a*R*,12***R***)-**1** (**Merck12-a2-2**) (6*R*,7*S*,7a*R*,12***S***)-**1'**

(6*S*,7*R*,7a*S*)-**17** (*R*)-**21** (6*S*,7*R*,7a*S*,12***S***)-**1** (6*S*,7*R*,7a*S*,12***R***)-**1'**

rac-**17** (*R*)-**21** *rac*-**1** *rac*-**1' (X-Ray)**

Although the absolute stereochemistry of the bicyclic scaffold was determined on the previous stages of the synthesis, the stereochemistry of the newly formed C-12 stereocenter was not known and could not be determined from the 2D NOESY NMR data. Compound **1** and its stereoisomers were obtained as viscous oils and attempts to crystallize them failed. We were fortunate to get single crystals of the racemate of the fast moving isomer, which turned out to be a diastereomer of Merck12-a2-2 (*rac*-**1'**). Thus, the relative and absolute configuration of all four obtained stereoisomers was unambiguously deduced from this X-Ray.

Conclusion

In conclusion, we accomplished the asymmetric synthesis of a potent hNK_1 antagonist Merck12-a2-2 (**1**) using selective CH-oxygenation of 1,2-oxazine-*N*-oxides via a tandem acylation/[3,3]-sigmatropic rearrangement process. The synthesis involved 10 steps in the longest sequence and afforded target product in ca. 5 % overall yield. Although we were not able to install the C-12 center stereoselectively, our strategy allows the assembly of the pyrrolooxazolidinone subunit of target molecule in a regio- and stereoselective manner. Using the developed strategy, we succeed in the synthesis of three stereoisomers of Merck12-a2-2, for which SAR studies will be performed in near future. The absolute stereochemistry of these stereoisomers was unambiguously determined by X-Ray analysis of intermediates and the final product.

We believe that the straightforward strategy described here is general and can be used to access enantiopure 3,4-disubstituted prolinols, which are frequently found in pharmaceutically relevant molecules and organocatalysts.

Experimental section

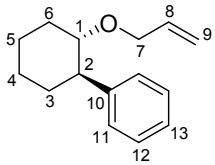
All reactions were carried out in oven-dried (150°C) glassware. The NMR spectra were recorded at room temperature with residual solvents peaks as an internal reference. The multiplicities are indicated by s (singlet), d (doublet), t (triplet), dd (doublet of doublets), q (quartet), quint (quintet), ddd (doublet of doublets of doublets), tt (triplet of triplets), tdd (triplets of doublets of doublets), m (multiplet), br (broad). The HRMS were measured on electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. Peaks in the FT-IR spectra data are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), sh (shoulder). Concentrations c in optical rotation angles are given in g/100 mL. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed using Kieselgel 40-60 μm 60A. Analytical thin-layer chromatography was performed on silica gel plates with QF 254. Visualization was accomplished with UV light and solution of anisaldehyde/H_2SO_4 in ethanol.

Chiral HPLC analysis was performed on a chromatograph with a UV-VIS photodiode array detector. The ozone/oxygen mixture was generated from dry oxygen (dried by Drierite column) using a laboratory-made ozone generator (ozone output 8-12 mmol/h)

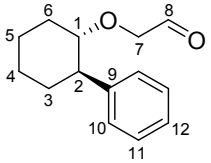
In most experiments, very similar yields in (+), (–) and racemic series were obtained if not otherwise stated. In Schemes and procedures, the best yields among three series are given.

Docking was performed using AutoDock Vina software[22] with using default parameters and the degree of exhaustiveness set to 16. For the docking the crystallographic structure of hNK_1 receptor with Aprepitant (PDB: 6HLO[9a]) was used. The receptor structure was prepared according to classical AutoDock scenario: ligand and water molecules were removed, polar hydrogens, Gasteiger-Huckel charges were added to protein (*pdbqt* input files of ligands were prepared using AutoDock Tools 1.5.6). The receptor model was verified by successful redocking of Aprepitant. 3D structures of ligands were generated using ChemBio3D Ultra 13.0 (MM2 force field for geometry optimization). Gasteiger charges and all the active torsions were added to the structures of ligands using AutoDock Tools 1.5.6 software. AutoGrid implemented in AutoDock Tools 1.5.6 was used for defining the active site. The grid (60 Å × 60 Å × 60 Å points) was centered on the co-crystallized ligand present in the complex. Top scored poses according to predicted free energy of binding were selected for further comparison and analysis of protein-ligand interactions (see Supporting information for details). Visualization of ligands in the binding site of hNK_1 receptor was done using Pymol v. 2.1.1.

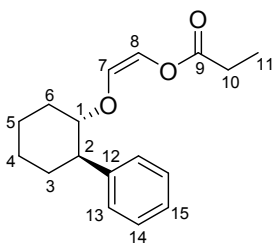
Steps (1) – (3): synthesis of chiral and racemic dienophile 7



3



4



7

Synthesis of (2-(allyloxy)cyclohexyl)benzene (3). Sodium hydride (510 mg, 12.73 mmol, *w*. ca. 60 % in mineral oil) was suspended in dry THF (20 mL) and the mixture was cooled to 0 °C. The solution of enantiopure or racemic *trans*-2-phenyl-1-cyclohexanol **2** (2.00 g, 11.35 mmol) in dry THF (20 mL) was added and the reaction mixture was stirred for 30 min at rt. Allyl bromide (1.1 mL, 12.48 mmol) was added and the reaction mixture was refluxed (silicone oil bath) under argon for 3.5 h. Then, additional portions of allyl bromide (0.55 mL, 6.24 mmol) and NaH (250 mg, 6.24 mmol, *w*. ca. 60 % in mineral oil) were added and the mixture was refluxed for another 5 h. The reaction mixture was cooled to rt, sat. aq. NH_4Cl solution (40 mL) was added, and the mixture was transferred into a separating funnel with sat. aq. NH_4Cl solution (60 mL) and MTBE (60 mL). The aqueous layer was extracted with MTBE (2×60 mL), and then the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane → Hexane/EtOAc = 20/1 → 10/1) to yield 2.42 g (99 %) of alkene **3**. R_f = 0.61 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.42 – 7.16 (m, 5H, *H11*, *H12* and *H13*), 5.63 (ddt, *J* = 19.1, 9.7, 5.5 Hz, 1H, *H8*), 5.07 – 5.00 (m, 1H, *H9'*), 5.00 – 4.94 (m, 1H, *H9''*), 3.84 (ddt, *J* = 12.9, 5.7, 1.5 Hz, 1H, *H7'*), 3.63 (ddt, *J* = 12.9, 5.6, 1.6 Hz, 1H, *H7''*), 3.40 (td, *J* = 10.0, 4.5 Hz, 1H, *H1*), 2.60 (ddd, *J* = 12.3, 10.1, 3.7 Hz, 1H, *H2*), 2.29 – 2.17 (m, 1H, *H6*'), 2.00 – 1.85 (m, 2H, *H3'* and *H5'*), 1.85 – 1.70 (m, 1H, *H4'*), 1.66 – 1.48 (m, 1H, *H3''*), 1.48 – 1.25 (m, 3H, *H4''*, *H5''* and *H6''*). ^{13}C{^{1}H} NMR (75 MHz, DEPT135, HSQC, $CDCl_3$) δ 144.9 (*C10*), 135.6 (*C8*), 128.2 and 127.9 (*C11* and *C12*), 126.1 (*C13*), 116.1 (*C9*), 81.7 (*C1*), 70.3 (*C7*), 51.4 (*C2*), 34.0 (*C3*), 32.7 (*C6*), 26.1 (*C4*), 25.2 (*C5*). HRMS (ESI): m/z calcd. for $[C_{15}H_{21}O]^+$ 217.1587, found 217.1596 $[M+H]^+$.

(+)-(*1R*,2*S*)-**3** (obtained from (+)-**2**): colorless oil, $[\alpha]_D$ = +66 (c = 1, EtOAc, 24 °C).

(−)-(1*S*,2*R*)-**3** (obtained from (−)-**2**): colorless oil, $[\alpha]_D$ = −64 (c = 1, EtOAc, 24 °C).

rac-**3** (obtained from *rac*-**2**): colorless oil.

Synthesis of 2-((2-phenylcyclohexyl)oxy)acetaldehyde (4). Allyl ether **3** (2.42 g, 11.2 mmol) was dissolved in dry DCM (40 mL) in a Schlenk flask, and the solution was cooled to −78 °C. The ozone was bubbled through the solution until it turned light blue (ca. 2 h). Then, oxygen was bubbled through the solution until the blue colour disappeared (ca. 20 min). The flask was filled with argon, and triphenylphosphine (4.4 g, 16.8 mmol) was added. The mixture was stirred for 20 min, being allowed to warm up to −40 °C, and then kept in a freezer for 16 h. The volatile components were then evaporated under reduced pressure, and the residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 20/1 → 10/1 → 5/1 → 3/1) to yield 1.97 g (81 %) of aldehyde **4**. R_f = 0.54 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, HMBC, $CDCl_3$) δ 9.29 (dd, *J* = 1.3, 1.1 Hz, 1H, *H8*), 7.37 – 7.20 (m, 5H, *H9*, *H10*, *H11*, *H12*), 3.81 (dd, *J* = 17.7, 1.1 Hz, 1H, *H7'*), 3.65 (dd, *J* = 17.7, 1.3 Hz, 1H, *H7''*), 3.39 (td, *J* = 10.0, 4.6 Hz, 1H, *H1*), 2.63 (ddd, *J* = 12.4, 10.0, 3.7 Hz, 1H, *H2*), 2.29 – 2.13 (m, 1H, *H6'*), 2.00 – 1.85 (m, 2H, *H3'* and *H5'*), 1.85 – 1.73 (m, 1H, *H4'*), 1.65 – 1.49 (m, 1H, *H3''*), 1.48 – 1.26 (m, 3H, *H4''*, *H5''* and *H6''*). ^{13}C{^{1}H} NMR (75 MHz, DEPT135, HSQC, HMBC, $CDCl_3$) δ 202.6 (*C8*), 144.2 (*C9*), 128.5 and 127.8 (*C10* and *C11*), 126.6 (*C12*), 84.3 (*C1*), 75.2 (*C7*), 51.3 (*C2*), 33.7 (*C3*), 32.6 (*C6*), 25.9 (*C4*), 25.1 (*C5*). HRMS (ESI): m/z calcd. for $[C_{14}H_{18}O_2Na]^+$ 241.1199, found 241.1203 $[M+Na]^+$.

(+)-(1*S*,2*R*)-**4** (obtained from (+)-**3**): colorless oil, $[\alpha]_D$ = +60 (c = 1, EtOAc, 24 °C).

(−)-(1*R*,2*S*)-**4** (obtained from (−)-**3**): colorless oil, $[\alpha]_D$ = −59 (c = 1, EtOAc, 24 °C).

rac-**4** (obtained from *rac*-**3**): colorless oil.

Synthesis of racemic 2-phenylcyclohexyl)oxy)methyl formate (6). Racemic allyl ether *rac*-**2** (2.21 g, 10.2 mmol) was dissolved in dry DCM (35 mL) in a Schlenk flask, and the solution was cooled to −78 °C. The ozone was bubbled through the solution until it turned light blue. Then, air was bubbled through the solution until the blue colour disappeared. Zinc powder (1.0 g, 15.3 mmol) was added followed by 50 % aqueous AcOH (33.8 mL). The suspension was allowed to warm to 0 °C, stirred for 30 minutes at 0 °C and then stirred for 2 h at rt. The reaction mixture

was diluted with DCM (100 mL) and washed with water (40 mL), sat. aq. $NaHCO_3$ solution (2 × 20 ml), and brine (20 mL). The aqueous layers were back-extracted with DCM (40 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (eluent: Hexane/EtOAc = 20/1 → 10/1 → 5/1) to give 0.64 g (27 %) of formate *rac*-**6** (fast moving fraction) and 0.76 g (34 %) of aldehyde *rac*-**4** (slow-moving fraction). R_f = 0.68 (Hexane/EtOAc = 3/1). Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.41 – 7.16 (m, 5H), 5.07 (d, *J* = 6.4 Hz, 1H), 4.90 (d, *J* = 6.4 Hz, 1H), 3.67 (ddd, *J* = 10.1, 10.1, 4.6 Hz, 1H), 2.56 (ddd, *J* = 10.9, 9.9, 3.5 Hz, 1H), 2.28 – 2.07 (m, 1H), 2.02 – 1.22 (m, 7H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 160.3 (CH), 143.6 (C), 128.1 (2 CH), 127.8 (2 CH), 126.3 (CH), 87.6 (CH_2), 83.2 (CH), 50.7 (CH), 33.2 (CH_2), 33.1 (CH_2), 25.6 (CH_2), 24.8 (CH_2). FT-IR (thin layer): 3029 (w), 2932 (s), 2859 (m), 1730 (s), 1602 (w), 1493 (m), 1450 (m), 1372 (w), 1163 (s), 1132 (s), 1080 (s), 967 (m, sh), 870 (s), 757 (m), 701 (m), 521 (m). HRMS (ESI): m/z calcd. for $[C_{14}H_{18}O_3K]^+$ 273.0888, found 273.0889 $[M+K]^+$.

Synthesis of (*Z*)-2-((2-phenylcyclohexyl)oxy)vinyl propionate (7). To a stirred solution of enantiopure or racemic aldehyde **4** (1.36 g, 6.23 mmol) in toluene (9 mL) were added propionic anhydride (8.0 mL, 62.3 mmol), KOH (37 mg, 0.66 mmol), and K_2CO_3 (4.30 g, 31.2 mmol). The mixture was refluxed (silicon oil bath) under argon for 6 h and then cooled to rt. Diethyl ether (40 mL) and sat. aq. Na_2CO_3 solution (60 mL) were added to the reaction mixture, and it was intensively stirred for 3 h. Then, the mixture was poured into a separating funnel containing diethyl ether (100 mL) and sat. aq. Na_2CO_3 solution (100 mL). The aqueous layer was washed with diethyl ether (2×50 mL), combined organic layers were washed with water (2×150 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 20/1 → 10/1) to yield 1.43 g (84 %) of alkene **7**. R_f = 0.70 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.35 – 7.17 (m, 5H, *H13*, *H14*, *H15*), 6.24 (d, *J* = 3.7 Hz, 1H, *H8*), 5.38 (d, *J* = 3.7 Hz, 1H, *H7*), 3.73 (td, *J* = 10.3, 4.4 Hz, 1H, *H1*), 2.73 (ddd, *J* = 12.3, 10.3, 3.8 Hz, 1H, *H2*), 2.39 (q,

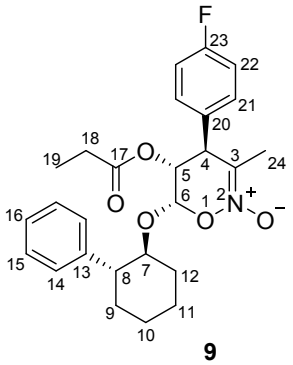
J = 7.6 Hz, 2H, *H10*), 2.30 – 2.13 (m, 1H, *H6'*), 2.01 – 1.85 (m, 2H, *H3'* and *H5'*), 1.85 – 1.71 (m, 1H, *H4'*), 1.68 – 1.47 (m, 2H, *H3''* and *H6''*), 1.47 – 1.28 (m, 2H, *H4''* and *H5''*), 1.15 (t, *J* = 7.6 Hz, 3H, *H11*). $^{13}C\{^{1}H\}$ NMR (75 MHz, HSQC, DEPT135, $CDCl_3$) δ 171.3 (*C9*), 143.4 (*C12*), 132.2 (*C7*), 128.3 and 127.8 (*C13* and *C14*), 126.5 (*C15*), 117.2 (*C8*), 85.6 (*C1*), 50.4 (*C2*), 33.7 (*C3*), 32.8 (*C6*), 27.3 (*C10*), 25.8 (*C4*), 25.0 (*C5*), 9.0 (*C11*). HRMS (ESI): m/z calcd. for $[C_{17}H_{23}O_3]^+$ 275.1642, found 275.1643 $[M+H]^+$.

(+)-(1*S*,2*R*)-**7** (obtained from (+)-**4**): colorless oil.

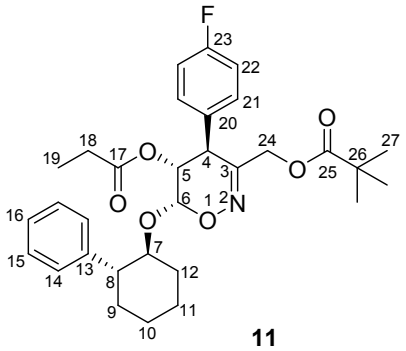
(−)-(1*R*,2*S*)-**7** (obtained from (−)-**4**): colorless oil, $[\alpha]_D = -123$ (c = 1, EtOAc, 25 °C).

rac-**7** (obtained from *rac*-**4**): colorless oil.

Steps (4) – (6)): synthesis and functionalization of 1,2-oxazine-*N*-oxide 9



9



11

(*E*)-1-Fluoro-4-(2-nitroprop-1-en-1-yl)benzene (8). To a stirred solution of 4-fluorobenzaldehyde (2.59 mL, 24.2 mmol) and nitroethane (2.61 mL, 36.3 mmol) in toluene (25 mL) was added *n*-butylamine (0.25 mL, 2.5 mmol). The mixture was refluxed with a Dean-Stark trap for ca. 6 h. The resulting dark-colored solution was kept in the fridge overnight and the resulting nitroalkene **8** was filtered off (1.77 g). Mother liquors were concentrated in vacuum and the residue was crystallized from methanol to give additionally 0.49 g of nitroalkene **8**. Overall yield: 2.26 g (52 %). Yellow solid. m.p. = 60 – 62 °C (MeOH). R_f = 0.71 (Hexane/EtOAc = 3/1). Lit.[23] 64 °C. NMR spectra are in agreement with literature data.[23]

4-(4-Fluorophenyl)-3-methyl-6-((2-phenylcyclohexyl)oxy)-5-(propionyloxy)-5,6-dihydro-4H-1,2-oxazine 2-oxide (9). Nitroalkene **8** (1.00 g, 5.52 mmol) was dissolved in dry DCM (30 mL) in a Schlenk flask under argon atmosphere, then CaH_2 (ca. 100 mg) was added and the

mixture was cooled to −94 °C (dry ice/acetone). Tin tetrachloride (720 μL, 6.16 mmol) was added and the mixture was stirred for 10 min. Then, a solution of enantiopure or racemic alkene **7** (1.85 g, 6.73 mmol) in dry DCM (15 mL) was added dropwise with intensive stirring. The reaction mixture was stirred at −94 °C for 2 h, then transferred into a separating funnel containing EtOAc (150 mL) and sat. aqueous Na_2CO_3 solution (150 mL). The aqueous layer was extracted with EtOAc (2×100 mL). The combined organic layers were washed with water (3×100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 10/1 → 5/1 → 3/1) to give 1.95 g (78 %) of nitronate **9** as a main fraction (d.r. ca. 30 : 1 by HPLC). The minor fraction contained 0.51 g (20 %) of a 5 : 1 mixture of nitronate **9** and its diastereomer **9'** with an opposite configuration of stereocenters in the 1,2-oxazine ring. Second column chromatography of the mixed fraction afforded additional 0.29 g (11 %) of a pure major diastereomer **9**. In case of the racemic nitronate synthesis, column chromatography was not required, and the residue from the aqueous work-up was crystallized from diethyl ether to yield 59 % of nitronate **9** (2.72 g from 1.84 g of nitroalkene **8**) after a single recrystallization. R_f = 0.19 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, HMBC, $CDCl_3$) δ 7.35 – 7.21 (m, 4H, *H14* and *H15*), 7.18 – 7.10 (m, 1H, *H16*), 7.05 – 6.91 (m, 4H, *H21* and *H22*), 5.64 (d, *J* = 3.0 Hz, 1H, $H6_{eq}$), 4.87 (dd, *J* = 10.2, 3.0 Hz, 1H, $H5_{ax}$), 4.14 (td, *J* = 10.5, 4.1 Hz, 1H, $H7_{ax}$), 3.31 (dq, *J* = 10.2, 1.7 Hz, 1H, $H4_{ax}$), 2.63 (ddd, *J* = 12.3, 10.5, 3.6 Hz, 1H, $H8_{ax}$), 2.19 (q, *J* = 7.6 Hz, 2H, *H18*), 2.33 – 2.05 (m, 1H, *H12'*), 1.94 – 1.82 (m, 2H, *H9'* and *H11'*), 1.81 – 1.68 (m, 1H, *H10'*), 1.66 – 1.46 (m, 1H, *H9''*), 1.46 – 1.21 (m, 3H, *H10''*, *H11''* and *H12''*), 1.19 (d, *J* = 1.7 Hz, 3H, *H24*), 1.00 (t, *J* = 7.6 Hz, 3H, *H19*). ^{13}C{^{1}H} NMR (75 MHz, HSQC, HMBC, DEPT135, $CDCl_3$) δ 173.4 (*C17*), 162.5 (d, *J* = 247.2 Hz, *C23*), 143.9 (*C13*), 132.8 (d, *J* = 3.3 Hz, *C20*), 130.2 (d, *J* = 8.3 Hz, *C21*), 128.4 and 127.7 (*C14* and *C15*), 126.2 (*C16*), 120.1 (*C3*), 116.1 (d, *J* = 21.7 Hz, *C22*), 94.0 (*C6*), 77.3 (*C7*), 70.4 (*C5*), 50.7 (*C8*), 44.4 (*C4*), 34.1 (*C9*), 30.2 (*C12*), 27.3 (*C18*), 26.0 (*C10*), 24.5 (*C11*), 16.9 (*C24*), 9.1 (*C19*). ^{19}F NMR (282 MHz,

$CDCl_3$) δ -114.5 (m). HRMS (ESI): m/z calcd. for $[C_{26}H_{31}FNO_5]^+$ 456.2181, found 456.2185 $[M+H]^+$. Elemental analysis: calcd. C, 68.55; H, 6.64; N, 3.07; found C, 68.32; H, 6.68; N, 3.16 (*rac*-**9**).

(+)-(4*S*,5*R*,6*S*,7*S*,8*R*)-**9** (obtained from (+)-(1*S*,2*R*)-**7**): yellowish foam, $[\alpha]_D$ = +304 (c = 1, EtOAc, 24 °C). HPLC analysis: ee > 99.5 % (RT 16.7 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/*i*-PrOH = 90 : 10; temperature 40°C; flow rate 1 mL/min).

(−)-(4*R*,5*S*,6*R*,7*R*,8*S*)-**9** (obtained from (−)-(1*R*,2*S*)-**7**): yellowish foam, $[\alpha]_D$ = −304 (c = 1, EtOAc, 23 °C). HPLC analysis: ee > 99.5 % (RT 9.2 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/*i*-PrOH = 90 : 10; temperature 40 °C; flow rate 1 mL/min).

rac-**9** (obtained from *rac*-**7**): white crystals, m.p. = 116.5 – 118.0 °C (Et_2O). Sample for single crystal X-Ray analysis was obtained by crystallization from diethyl ether. CCDC 1987344 contains the supplementary crystallographic information for *rac*-**9**.

Characteristic NMR data of minor diastereomer *rel*-(4*S*,5*R*,6*S*,7*R*,8*S*)-**9'** (in mixture with major isomer **9**). ^{1}H NMR (300 MHz, $CDCl_3$, characteristic signals) δ 4.99 (d, *J* = 3.0 Hz, 1H), 4.74 (dd, *J* = 9.8, 3.0 Hz, 1H), 4.00 (td, *J* = 10.3, 4.6 Hz, 1H), 3.73 (dd, *J* = 9.9, 1.7 Hz, 1H), 0.87 (t, *J* = 7.5 Hz, 3H).

(4-(4-Fluorophenyl)-6-((2-phenylcyclohexyl)oxy)-5-(propionyloxy)-5,6-dihydro-4H-1,2-oxazin-3-yl)methyl pivalate (11). Enantiopure or racemic nitronate **9** (3.68 g, 8.08 mmol) was dissolved in dry acetonitrile (18 mL) in a Schlenk flask under argon atmosphere, then NEt_3 (2.3 mL, 16.52 mmol) was added. The reaction mixture was cooled to −30 °C and pivaloyl chloride (1.5 mL, 12.2 mmol) was added. The reaction mixture was stirred at ca. −30 °C for 1 h, then kept in a fridge (ca. 0 °C) for 20 h. The mixture was transferred into a separating funnel containing MTBE (200 mL) and 0.25 M aq. $NaHSO_4$ solution (100 mL). The aqueous layer was extracted with MTBE (2×100 mL), then the combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 10/1) to yield 4.18 g

(96 %) of pivalate **11**. R_f = 0.71 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, HMBC, $CDCl_3$) δ 7.34 – 7.14 (m, 5H, *H14*, *H15* and *H16*), 7.12 – 6.91 (m, 4H, *H21* and *H22*), 5.43 (d, *J* = 2.9 Hz, 1H, $H6_{eq}$), 4.97 (dd, *J* = 10.8, 2.9 Hz, 1H, $H5_{ax}$), 4.07 – 3.91 (m, 1H, *H7*), 3.99 (d, *J* = 4.7 Hz, 2H, *H24*), 3.34 (d, *J* = 10.8 Hz, 1H, $H4_{ax}$), 2.64 (ddd, *J* = 12.3, 10.6, 3.7 Hz, 1H, $H8_{ax}$), 2.21 (qd, *J* = 7.7, 5.5 Hz, 2H, *H18*), 2.31 – 2.13 (m, 1H, *H12'*), 2.00 – 1.85 (m, 2H, *H9'* and *H11'*), 1.85 – 1.74 (m, 1H, *H10'*), 1.67 – 1.45 (m, 1H, *H9''*), 1.45 – 1.20 (m, 3H, *H10''*, *H11''* and *H12''*), 1.10 (s, 9H, *H27*), 1.02 (t, *J* = 7.7 Hz, 3H, *H19*). ^{13}C{^{1}H} NMR (75 MHz, HSQC, HMBC, DEPT135, $CDCl_3$) δ 177.4 (*C25*), 173.5 (*C17*), 162.4 (d, *J* = 247.4 Hz, *C23*), 154.3 (*C3*), 144.0 (*C13*), 131.5 (d, *J* = 3.4 Hz, *C20*), 130.6 (d, *J* = 8.1 Hz, *C21*), 128.2 and 127.9 (*C14* and *C15*), 126.2 (*C16*), 116.0 (d, *J* = 21.6 Hz, *C22*), 91.0 (*C6*), 78.0 (*C7*), 70.8 (*C5*), 63.0 (*C24*), 50.4 (*C8*), 40.7 (*C4*), 38.7 (*C26*), 34.3 (*C9*), 31.0 (*C12*), 27.4 (*C18*), 27.2 (*C27*), 26.1 (*C10*), 24.8 (*C11*), 9.2 (*C19*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -114.8 (m). HRMS (ESI): m/z calcd. for $[C_{31}H_{39}FNO_6]^+$ 540.2756, found 540.2755 $[M+H]^+$.

(+)-(4*S*,5*R*,6*S*,7*S*,8*R*)-**11** (obtained from (+)-**9**): yellowish oil, $[\alpha]_D$ = +280 (c = 1, EtOAc, 24 °C).

(−)-(4*R*,5*S*,6*R*,7*R*,8*S*)-**11** (obtained from (−)-**9**): yellowish oil, $[\alpha]_D$ = −288 (c = 1, EtOAc, 23 °C).

rac-**11** (obtained from *rac*-**9**): yellowish oil.

(4-(4-Fluorophenyl)-6-((2-phenylcyclohexyl)oxy)-5-(propionyloxy)-1,2-oxazinan-3-yl)methyl pivalate (12). To an intensively stirred solution of enantiopure or racemic 5,6-dihydro-4*H*-1,2-oxazine **11** (1.31 g, 2.43 mmol) in acetic acid (10 mL) was added sodium cyanoborohydride (0.92 g, 14.64 mmol) under argon. The reaction mixture was stirred at rt for 1.5 h, then sat. aq. $NaHCO_3$ solution (150 mL) and EtOAc (50 mL) were carefully added, and the mixture was poured into a separating funnel containing EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2×50 mL), the combined organic layers were washed with sat. aq. $NaHCO_3$ solution (2×100 mL), water (100 mL) and brine (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure to dryness. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 5/1 → 3/1) to yield 1.14 g (87 %) of oxazine **12**

in a mixture with C-6 epimer (d.r. **12**/**12'** = 5 : 1). Pure fraction of **12** was obtained by second column chromatography. In case of the racemic synthesis, column chromatography was not required, and the residue after aqueous work-up was crystallized from methanol to yield 77 % of 1,2-oxazine *rac*-**12** (contained no epimer). R_f = 0.30 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, HMBC, NOESY, $CDCl_3$) δ 7.40 – 7.33 (m, 4H, *H14* and *H15*), 7.26 – 7.15 (m, 1H, *H16*), 7.07 (m, 2H, *H21*), 6.94 (m, 2H, *H22*), 5.07 (d, *J* = 3.5 Hz, 1H, $H6_{eq}$), 4.94 (dd, *J* = 11.5, 3.5 Hz, 1H, $H5_{ax}$), 4.13 (d, *J* = 12.8 Hz, 1H, *NH*), 3.74 (td, *J* = 10.3, 4.2 Hz, 1H, $H7_{ax}$), 3.48 (dd, *J* = 11.7, 2.7 Hz, 1H, *H24'*), 3.31 (dddd, *J* = 12.8, 10.3, 7.2, 2.7 Hz, 1H, $H3_{ax}$), 3.19 (dd, *J* = 11.7, 7.2 Hz, 1H, *H24''*), 2.70 (ddd, *J* = 12.6, 10.3, 3.9 Hz, 1H, $H8_{ax}$), 2.61 (dd, *J* = 11.5, 10.3 Hz, 1H, $H4_{ax}$), 2.08 (q, *J* = 7.7 Hz, 2H, *H18*), 2.07 – 1.90 (m, 2H, *H9'* and *H12'*), 1.90 – 1.72 (m, 2H, *H10'* and *H11'*), 1.69 – 1.47 (m, 1H, *H9''*), 1.33 (m, 3H, *H10''*, *H11''* and *H12''*), 1.10 (s, 9H, *H27*), 0.91 (t, *J* = 7.6 Hz, 3H, *H19*). ^{13}C{^{1}H} NMR (75 MHz, HSQC, HMBC, DEPT135, $CDCl_3$) δ 178.0 (*C25*), 173.7 (*C17*), 162.1 (d, *J* = 245.8 Hz, *C23*), 144.3 (*C13*), 133.0 (d, *J* = 3.1 Hz, *C20*), 129.5 (d, *J* = 7.2 Hz, *C21*), 129.0 (*C14* or *C15*), 127.9 (*C14* or *C15*), 127.1 (*C16*), 115.7 (d, *J* = 21.4 Hz, *C22*), 93.6 (*C6*), 79.7 (*C7*), 72.4 (*C5*), 62.8 (*C24*), 60.5 (*C3*), 50.7 (*C8*), 42.6 (*C4*), 38.7 (*C26*), 33.8 (*C9*), 31.7 (*C12*), 27.4 (*C18*), 27.2 (*C27*), 26.0 (*C10*), 24.8 (*C11*), 9.1 (*C19*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.9 (m). Characteristic 2D NOESY correlations: $H3_{ax}$/$H5_{ax}$. HRMS (ESI): m/z calcd. for $[C_{31}H_{41}FNO_6]^+$ 542.2912, found 542.2906 $[M+H]^+$.

(+)-(3*R*,4*S*,5*R*,6*S*,7*S*,8*R*)-**12** (obtained from (+)-**11**): white foam, $[\alpha]_D$ = +210 (c = 1, EtOAc, 23 °C).

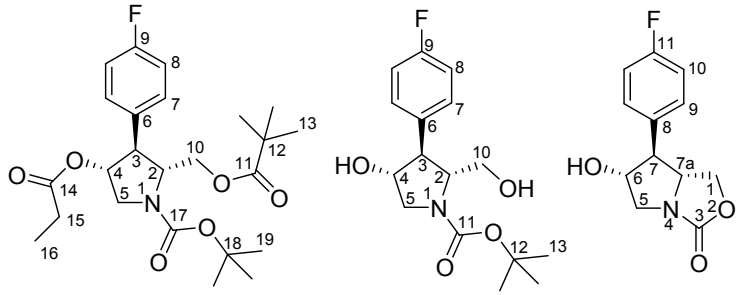
(−)-(3*S*,4*R*,5*S*,6*R*,7*R*,8*S*)-**12** (obtained from (−)-**11**): white foam, $[\alpha]_D$ = −200 (c = 1, EtOAc, 25 °C).

rac-**12** (obtained from *rac*-**11**): white crystals, m.p. = 135.5 − 136.5 °C (CH_3OH).

Characteristic NMR data of C-6 epimer **12'** (in a mixed fraction with **12**, **12**/**12'** = 3 : 1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (br d, *J* = 10.7 Hz, 1H), 5.46 (d, *J* = 3.5 Hz, 1H), 5.02 (dd, *J* =

11.6, 3.5 Hz, 1H), 4.01 (ddd, *J* = 10.4, 10.4, 4.1 Hz, 1H), 3.74 (d, *J* = 13.3 Hz, 1H), 3.66 (br ddd, *J* = 11.8, 10.7, 4.0 Hz, 1H), 3.48 (d, *J* = 13.3, 4.4 Hz, 1H), 2.97 (dd, *J* = 11.8, 11.6 Hz, 1H).

Steps (7) – (9): synthesis of pyrrolooxazolidinones 17



15 **16** **17**

***Tert*-butyl 3-(4-fluorophenyl)-2-((pivaloyloxy)methyl)-4-(propionyloxy)pyrrolidine-1-carboxylate (15).** A solution of enantiopure or racemic 1,2-oxazine **12** (0.40 g, 0.738 mmol) and Boc_2O (490 mg, 2.25 mmol) in methanol (1.5 mL) was placed in a glass vial. A suspension of Raney nickel (ca. 100 mg) in methanol (ca. 1 mL) was added. The reaction vial was placed in a steel autoclave, that was then flushed and filled with hydrogen to a pressure of 45 bar and heated to 45 − 50 °C. The hydrogenation was conducted for 2 h with intensive stirring. Then, the autoclave was cooled to rt and evacuated, the catalyst was removed using a magnet and washed with methanol several times. The solution was concentrated to dryness under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 20/1→10/1) to yield 0.226 g (68 %) of *N*-Boc pyrrolidine **15**. The column was then washed with Hexane/EtOAc = 5/1 to collect the recovered *trans*-2-phenylcyclohexanol (0.118 g, 91 %). R_f = 0.76 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, 320 K, $CDCl_3$) δ 7.22 – 7.11 (m, 2H, *H7*), 7.07 – 6.92 (m, 2H, *H8*), 5.18 – 4.95 (m, 1H, *H4*), 4.44 – 4.17 (m, 2H, *H10*), 4.15 – 3.87 (m, 2H, *H2* and *H5'*), 3.46 – 3.23 (m, 2H, *H3* and *H5''*), 2.33 (q, *J* = 7.5 Hz, 2H, *H15*), 1.49 (s, 9H, *H19*), 1.15 (s, 9H, *H13*), 1.11 (t, *J* = 7.6 Hz, 3H, *H16*). ^{13}C{^{1}H} NMR (75 MHz, HSQC, 320 K, $CDCl_3$) δ 178.1 (*C11*), 173.9 (*C14*), 162.3 (d, *J* = 246.4 Hz, *C9*), 154.1 (*C17*), 135.2 (*C6*), 129.0 (d, *J* = 8.1 Hz, *C7*), 116.0 (d, *J* = 21.4 Hz, *C8*), 80.8 (*C18*), 77.4 (*C4*), 63.5 (*C10*), 61.3 (*C2*), 51.4 (*C3*), 50.9 (*C5*), 39.0 (*C12*), 28.6 (*C19*), 27.7 (*C15*), 27.3 (*C13*), 9.0 (*C16*). ^{19}F

NMR (282 MHz, $CDCl_3$) δ -115.8 (m), -115.9 (m). Signal of fluorine appears as two singlets due to the presence of N-Boc rotamers. HRMS (ESI): m/z calcd. for $[C_{24}H_{35}FNO_6]^+$ 452.2443, found 452.2431 $[M+H]^+$.

(+)-(2*R*,3*S*,4*R*)-**15** (obtained from (+)-**12**): colorless oil , $[\alpha]_D^{24}$ = +0.3 (c = 1, EtOAc, 24 °C).

(−)-(2*S*,3*R*,4*S*)-**15** (obtained from (−)-**12**): colorless oil, $[\alpha]_D^{24}$ = −0.3 (c = 1, EtOAc, 28 °C).

rac-**15** (obtained from *rac*-**12**): colorless oil.

***Tert*-butyl 3-(4-fluorophenyl)-4-hydroxy-2-(hydroxymethyl)pyrrolidine-1-carboxylate (16).** Enantiopure or racemic pyrrolidine **15** (151 mg, 0.334 mmol) was treated with 1M solution of potassium hydroxide in methanol/water = 1 : 1 mixture (6.7 mL, 6.7 mmol). The reaction mixture was stirred at rt for 24 h, then the solvent was evaporated under reduced pressure and the residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 1/1 → EtOAc) to yield 81 mg (78 %) of diol **16**. R_f = 0.61 (EtOAc). ^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.17 – 7.11 (m, 2H, *H7*), 7.05 – 6.97 (m, 2H, *H8*), 4.09 (dd, *J* = 6.1, 4.6 Hz, 1H, *H4*), 4.04 – 3.91 (m, 2H, *H10*), 3.85 (dd, *J* = 11.8, 6.1 Hz, 1H, *H5'*), 3.79 (s, 2H, both *OH*), 3.66 (dd, *J* = 11.4, 4.2 Hz, 1H, *H2*), 3.34 (dd, *J* = 11.8, 4.6 Hz, 1H, *H5''*), 3.07 (br s, 1H, *H3*), 1.48 (s, 9H, *H13*). ^{13}C{^{1}H} NMR (75 MHz, COSY, HSQC, $CDCl_3$) δ 162.1 (d, *J* = 245.0 Hz, *C9*), 156.1 (*C11*), 135.4 (*C6*), 129.1 (*C7*), 116.0 (d, *J* = 21.3 Hz, *C8*), 80.9 (*C12*), 75.7 (*C4*), 65.4 (*C10*), 64.9 (*C2*), 55.3 (*C3*), 54.0 (*C5*), 28.6 (*C13*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.2 (m). HRMS (ESI): m/z calcd. for $[C_{16}H_{23}FNO_4]^+$ 312.1606, found 312.1606 $[M+H]^+$.

(+)-(2*R*,3*S*,4*R*)-**16** (obtained from (+)-**15**): colorless oil, $[\alpha]_D$ = +17 (c = 1, EtOAc, 25 °C).

(−)-(2*S*,3*R*,4*S*)-**16** (obtained from (−)-**15**): colorless oil, $[\alpha]_D$ = −21 (c = 1, EtOAc, 27 °C).

rac-**16** (obtained from *rac*-**15**): colorless oil.

***Rel*-(2*R*,3*S*,4*R*)-3-(4-fluorophenyl)-2-((pivaloyloxy)methyl)-4-(propionyloxy)pyrrolidin-1-ium trifluoroacetate (*rac*-18).** To a stirred solution of *rac*-**15** (280 mg, 0.62 mmol) in DCM (4.2 mL) was added CF_3COOH (0.96 mL, 12.6 mmol) at 0 °C. The mixture was stirred at this temperature for 2 h, and then concentrated under reduced pressure. The residue was treated with

diethyl ether to give 251 mg (86 %) of the trifluoroacetate salt *rac*-**18** as white solid. m.p. = 145.5 − 152.0 °C (Et_2O). ^{1}H NMR (300 MHz, COSY, HSQC, HMBC, NOESY, $CDCl_3$) δ 11.0 − 9.5 (br, 2H, *NH*), 7.27 (m, 2H, *H7*), 7.12 (m, 2H, *H8*), 5.25 (dd, *J* = 11.1, 6.8 Hz, 1H, *H4*), 4.36 (d, *J* = 4.7 Hz, 2H, *H10*), 3.97 (dt, *J* = 9.6, 4.7 Hz, 1H, *H2*), 3.86 (dd, *J* = 12.8, 6.8 Hz, 1H, *H5'*), 3.45 (m, 2H, *H3* and *H5''*), 2.35 (q, *J* = 7.5 Hz, 2H, *H15*), 1.18 (s, 9H, *H13*), 1.11 (t, *J* = 7.5 Hz, 3H, *H16*). ^{13}C{^{1}H} NMR (75 MHz, HSQC, HMBC, DEPT135, $CDCl_3$) δ 178.2 (*C11*), 173.9 (*C14*), 167.6 (*CF_3COO*), 162.6 (q, *J* = 75 Hz, *CF_3COO*), 162.8 (d, *J* = 248 Hz, *C9*), 131.0 (*C6*), 129.4 (d, *J* = 8.2 Hz, *C7*), 116.6 (d, *J* = 21.7 Hz, *C8*), 77.1 (*C4*), 62.5 (*C2*), 61.3 (*C10*), 51.0 (*C3*), 49.2 (*C5*), 38.9 (*C12*), 27.1 (*C15*), 26.9 (*C13*), 8.8 (*C16*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -76.4 (s), -113.8 (m). Characteristic 2D NOESY correlations: *H4*/*H7*, *H7*/*H2*. HRMS (ESI): m/z calcd. for $[C_{19}H_{27}FNO_4]^+$ 352.1919, found 352.1917 $[M\text{-}CF_3COO]^+$.

7-(4-Fluorophenyl)-6-hydroxytetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (17). *Method 1:* Enantiopure or racemic diol **16** (29.5 mg, 0.095 mmol) was dissolved in DCM (0.95 mL), and the solution was cooled to 0 °C. Trifluoroacetic acid (0.15 mL, 1.96 mmol) was added, and the mixture was stirred for 30 min under argon atmosphere, then the volatile components were removed under reduced pressure. The residue was dried in vacuum until constant weight and then dissolved in dry acetonitrile (0.60 mL). The resulting solution was cooled to 0 − 5 °C, then a solution of triphosgene (14 mg, 0.047 mmol) in dry acetonitrile (0.35 mL) and triethylamine (0.070 mL, 0.50 mmol) were added. The reaction mixture was stirred at 0 °C for 1 h, and the volatile components were removed under reduced pressure. The residue was subjected to a chromatography on preparative TLC-plate (eluent: EtOAc) to yield 13.5 mg (60 %) of target pyrrolooxazolone **17**.

Method 2: Racemic trifluoroacetate *rac*-**18** (750 mg, 1.61 mmol) was treated with 32 mL of 1M solution of KOH in MeOH/H_2O (1 : 1). The mixture was stirred for 9 h at rt and then kept overnight without stirring. The resulting solution was cooled to 0 − 5 °C and 4 M solution of HCl in dioxane (32 mL) was added. After 20 min of stirring, volatiles were removed under

reduced pressure. Acetonitrile (5 mL) was added and the mixture was concentrated again. The residue was dried in vacuum and triturated with pentane (2 × 20 mL) to remove carboxylic acids. The remaining solid was dried in vacuum and treated with MeCN (2 × 15 mL) and then MeOH (2 × 15 mL). The insoluble material (inorganic salts) was filtered off, and the combined organic extracts were concentrated under reduced pressure. The residual solid (crude hydrochloride salt *rac*-**19**) was dried in vacuum and then dissolved in dry MeCN (6 mL). The solution was cooled to 0 − 5 °C and a solution of triphosgene (240 mg, 0.81 mmol) in MeCN (5 ml) was added followed by Et_3N (1.12 ml, 8.05 mmol). The mixture was stirred at this temperature for 20 minutes and then allowed to warm to rt. After stirring for 2.5 h at rt, the mixture was concentrated under reduced pressure and the residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 5/1→1/1→ EtOAc) to yield 208 mg (55 % based on *rac*-**18**) of target pyrrolooxazolone *rac*-**17**.[24]

R_f = 0.67 (EtOAc/methanol = 10/1). ^{1}H NMR (300 MHz, COSY, HSQC, HMBC, NOESY, $CDCl_3$) δ 7.23 – 7.14 (m, 2H, *H9*), 7.09 – 6.97 (m, 2H, *H10*), 4.52 – 4.40 (m, 1H, *H6*), 4.46 (dd, *J* = 9.0, 8.4 Hz, 1H, *H1'*), 4.23 (dd, *J* = 9.0, 3.7 Hz, 1H, *H1''*), 4.04 (ddd, *J* = 9.0, 8.4, 3.7 Hz, 1H, *H7a*), 3.60 (d, *J* = 5.7 Hz, 2H, *H5*), 3.56 (br, 1H, *OH*), 3.00 (dd, *J* = 9.0, 6.8 Hz, 1H, *H7*). ^{13}C{^{1}H} NMR (75 MHz, HSQC, HMBC, DEPT135, $CDCl_3$) δ 162.3 (d, *J* = 246.6 Hz, *C11*), 162.2 (*C3*), 133.2 (d, *J* = 3.1 Hz, *C8*), 129.3 (d, *J* = 8.0 Hz, *C9*), 116.1 (d, *J* = 21.3 Hz, *C10*), 79.9 (*C6*), 67.6 (*C1*), 64.0 (*C7a*), 57.7 (*C7*), 53.7 (*C5*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.4 (m). Characteristic 2D NOESY correlations: *H7a/H9, H6/H9*. HRMS (ESI): m/z calcd. for $[C_{12}H_{13}FNO_3]^+$ 238.0874, found 238.0874 $[M+H]^+$.

(+)-(6*R*,7*S*,7a*R*)-**17** (obtained from (+)-**16**): white crystals, m.p. = 165.0 − 166.5 °C (Et_2O), $[\alpha]_D$ = +12 (c = 0.5, EtOH 96 %, 24 °C). HPLC analysis: ee > 99.5 % (RT 6.7 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/i-PrOH = 80 : 20; temperature 40 °C; flow rate 1 ml/min).

(−)-(6*S*,7*R*,7a*S*)-**17** (obtained from (−)-**16**): white crystals, $[\alpha]_D$ = −16 (c = 0.5, EtOH 96 %, 29 °C). HPLC analysis: ee 98 % (RT 10.6 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/i-PrOH = 80 : 20; temperature 40 °C; flow rate 1 ml/min).

rac-**17** (obtained from *rac*-**16** or *rac*-**18**): yellowish oil.

Synthesis of 3,5-bis(trifluoromethyl)phenyl)ethyl imidates

(*S*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethan-1-ol. To a stirred solution of (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol (50 mg, 0.19 mmol), *p*-nitrobenzoic acid (130 mg, 0.77 mmol) and PPh_3 (203 mg, 0.77 mmol) in dry THF (1.5 mL) were added a solution of DEAD in toluene (*w.* 40 %, 0.35 mL, 0.7 mmol) at 0 °C under argon atmosphere. The mixture was allowed to warm to rt and stirred for 3 h. Then, it was transferred into a separating funnel containing MTBE (50 mL) and sat. aq. $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with MTBE (2×20 mL). Combined organic layers were washed with sat. aq. $NaHCO_3$ solution (50 mL), water (50 mL) and brine (50 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 20/1 → 10/1 → 5/1 → 3/1 → 1/1) to give 105 mg of an inseparable mixture of (*S*)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl 4-nitrobenzoate and DEAD. The mixture was treated with 5.2 mL of 1M KOH solution in MeOH/H_2O (1 : 1), and the solution was stirred at rt overnight. Then, methanol was evaporated under reduced pressure, the residue was transferred into a separating funnel containing EtOAc (50 mL) and sat. aq. NH_4Cl solution (50 mL). The aqueous layer was extracted with EtOAc (2×25 mL). Combined organic layers were washed with water (50 mL) and brine (50 mL), then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 5/1 → 3/1) to give (*S*)-1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol. Yield: 18 mg (36 % based on (*R*)-enantiomer). White solid. mp 55 – 60 °C, lit. 53 – 58 °C ((*R*)-enantiomer, Sigma-Aldrich). R_f = 0.5 (Hexane/EtOAc = 3/1). $[\alpha]_D$ = −24 (c = 1, EtOAc, 26 °C), lit.[25] −24.8 (c = 1, $CHCl_3$, 20 °C). ^{1}H NMR spectrum is in agreement with an authentic sample of (*R*)-enantiomer. HPLC analysis:

ee > 99 % (RT 4.9 min; column CHIRALPAK OD-3 (15 cm); solvent Hexane/i-PrOH = 98 : 2; temperature 40 °C; flow rate 1 ml/min).

1-(3,5-Bis(trifluoromethyl)phenyl)ethyl 2,2,2-trichloroacetimidate (20). Enantiomeric imidates (*R*)-**20** and (*S*)-**20** were prepared from (*R*)- and (*S*)-1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol, respectively, by treatment with trichloroacetonitrile and DBU following the previously described procedure.[8d] R_f = 0.6 (Hexane/EtOAc = 4/1). ^{1}H NMR spectra of **20** are in agreement with literature data.[8d]

(*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl 2,2,2-trifluoro-*N*-phenylacetimidate ((*R*)-21). (*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethan-1-ol (200 mg, 0.775 mmol) was dissolved in acetone (15 mL), then K_2CO_3 (161 mg, 1.17 mmol) and 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride (150 μL, 0.930 mmol) were added. The reaction mixture was stirred at rt for 20 h, then filtered through Celite and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (Eluent: Hexane → Hexane/EtOAc = 20:1) to yield 278 mg (84%) of imidate (*R*)-**21** as a yellow-green solid. R_f = 0.58 (Hexane/EtOAc = 10/1). m. p. = 54.5 – 56 °C. $[\alpha]_D$ = +108 (c = 1, EtOAc, 23 °C). ^{1}H NMR (300 MHz, HMBC, $CDCl_3$) δ 7.87 (s, br, 1H, HC_{Ar}), 7.86 (s, br, 2H, HC_{Ar}), 7.32 – 7.23 (m, 2H, *m*-HC_{Ph}), 7.14 – 7.02 (m, 1H, *p*-HC_{Ph}), 6.71 – 6.61 (m, 2H, *o*-HC_{Ph}), 6.11 (q, *J* = 6.6 Hz, 1H, *HC*-*O*), 1.74 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (75 MHz, HMBC, DEPT135, $CDCl_3$) δ 143.8 (C_{Ar}), 143.7 (C_{Ar}), 132.2 (q, *J* = 33.7 Hz, =*C*-CF_3), 128.9 (*m*-HC_{Ph}), 126.5 (m, HC_{Ar}), 124.4 (*p*-HC_{Ph}), 123.3 (q, *J* = 272.8 Hz, 2 CF_3), 122.2 (m, HC_{Ar}), 119.4 (*o*-HC_{Ph}), 116.1 (q, *J* = 287.6 Hz, CF_3), 74.4 (*HC*-*O*), 22.1 (CH_3). *C*=*N* is not observed. ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.8 (2 CF_3), -66.7 (CF_3). HRMS (ESI): m/z calcd. for $[C_{18}H_{13}F_9NO]^+$ 430.0848, found 430.0850 $[M+H]^+$.

Step 10: Synthesis of 6-(1-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-7-(4-fluorophenyl)tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one (1 and 1'). To a stirred solution of enantiopure or racemic pyrrolo[1,2-c]oxazol-3-one **17** (10 mg, 0.042 mmol) and imidate (*R*)-**22** (24 mg, 0.056 mmol) in dry CH_2Cl_2 (0.5 mL) were added molecular sieves AW-300 (15 mg,

dried in vacuum with heating) under argon atmosphere). The mixture was stirred for 20 min and then cooled to 0 – 5 °C (ice water bath). TMSOTf (10 μL, 0.056 mmol) was added through septa and the reaction mixture was stirred at 0°C for 3 h. Then, additional portions of imidate (*R*)-**21** (23 mg. 0.054 mmol) and TMSOTf (10 μL, 0.056 mmol) were added. The mixture was stirred at 0 °C for 10 min, and then at rt for 2 h. Then, CH_2Cl_2 (2 mL) and sat. aq. soln. of $NaHCO_3$ (1 mL) were added and the resulting mixture was stirred for 5 min. The organic layer was separated, the aqueous layer was washed with CH_2Cl_2 (2×2 mL). Combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to a preparative thin-layer chromatography (eluent: Hexane/EtOAc = 3/1, 2 runs). Two fractions were collected: the slow moving fraction was Merck12-a2-2 (compound **1**, 6.7 mg), while the fast moving one was its diastereomer (compound **1'**, 6.7 mg). Combined yield of two diastereomers – 67 % (d.r. = 1 : 1).

Diastereomer 1. R_f = 0.30 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.71 (s, 1H, *H17*), 7.48 (s, 2H, *H15*), 7.08 – 7.00 (m, 2H, *H9*), 6.99 – 6.91 (m, 2H, *H10*), 4.51 (q, *J* = 6.4 Hz, 1H, *H12*), 4.44 (dd, *J* = 9.2, 7.9 Hz, 1H, *H1'*), 4.21 (dd, *J* = 9.2, 3.2 Hz, 1H, *H1''*), 4.04 (ddd, *J* = 6.8, 6.3, 4.2 Hz, 1H, *H6*), 3.95 (ddd, *J* = 9.2, 7.9, 3.2 Hz, 1H, *H7a*), 3.84 (dd, *J* = 12.1, 4.2 Hz, 1H, *H5'*), 3.59 (dd, *J* = 12.1, 6.3 Hz, 1H, *H5''*), 3.05 (dd, *J* = 9.2, 6.8 Hz, 1H, *H7*), 1.41 (d, *J* = 6.4 Hz, 3H, *H13*). ^{13}C{^{1}H} NMR (75 MHz, HSQC, $CDCl_3$) δ 162.5 (d, *J* = 247.5 Hz, C11), 161.6 (C3), 145.8 (*C14*), 132.4 (d, *J* = 3.4 Hz, *C8*), 132.1 (q, *J* = 33.5 Hz, *C16*), 129.0 (d, *J* = 8.1 Hz, *C9*), 126.1 (*C15*), 123.2 (q, *J* = 272.9 Hz, *C18*), 121.9 (*C17*), 116.3 (d, *J* = 21.5 Hz, *C10*), 85.1 (*C6*), 76.6 (*C12*), 66.9 (*C1*), 63.8 (*C7a*), 56.7 (*C7*), 51.6 (*C5*), 24.8 (*C13*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.7 (s, CF_3), -114.9 (m, CF). HRMS (ESI): m/z calcd. for $[C_{22}H_{19}FNO_3]^+$ 478.1248, found 478.1242 $[M+H]^+$. For numeration of atoms see Scheme 8.

(+)-(6*R*,7*S*,7a*R*,12*R*)-**1** (Merck12-a2-2, obtained from (+)-(6*R*,7*S*,7a*R*)-**17**): colorless oil. HPLC analysis: ee 97 % (RT 23.3 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/i-PrOH = 98 : 2; temperature 40 °C; flow rate 1 ml/min).

(−)-(6*S*,7*R*,7a*S*,12*S*)-**1** (obtained from (−)-(6*S*,7*R*,7a*S*)-**17**): colorless oil. $[\alpha]_D$ = −52 (c = 0.5, EtOAc, 25 °C). HPLC analysis: ee 97 % (RT 19.0 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/i-PrOH = 98 : 2; temperature 40 °C; flow rate 1 ml/min).

rac-**1** (obtained from *rac*-**17**): colorless oil.

Diastereomer 1'. R_f = 0.42 (Hexane/EtOAc = 3/1). ^{1}H NMR (300 MHz, COSY, HSQC, $CDCl_3$) δ 7.77 (s, 1H, *H17*), 7.44 (s, 2H, *H15*), 7.20 – 7.13 (m, 2H, *H9*), 7.13 – 7.04 (m, 2H, *H10*), 4.40 (dd, *J* = 9.2, 7.8 Hz, 1H, *H1'*), 4.35 (q, *J* = 6.4 Hz, 1H, *H12*), 4.21 – 4.09 (m, 1H, *H6*), 4.18 (dd, *J* = 9.2, 3.0 Hz, 1H, *H1''*), 3.90 (ddd, *J* = 10.0, 7.8, 3.0 Hz, 1H, *H7a*), 3.68 (dd, *J* = 12.3, 5.0 Hz, 1H, *H5'*), 3.49 (dd, *J* = 12.3, 7.4 Hz, 1H, *H5''*), 3.05 (dd, *J* = 10.0, 7.2 Hz, 1H, *H7*), 1.32 (d, *J* = 6.4 Hz, 3H, *H13*). ^{13}C{^{1}H} NMR (75 MHz, HSQC, $CDCl_3$) δ 162.6 (d, *J* = 247.7 Hz, *C11*), 161.2 (*C3*), 145.5 (*C14*), 133.2 (d, *J* = 3.4 Hz, *C8*), 132.1 (q, *J* = 33.3 Hz, *C16*), 129.1 (d, *J* = 8.1 Hz, *C9*), 126.4 (*C15*), 123.3 (q, *J* = 272.9 Hz, *C18*), 122.0 (*C17*), 116.6 (d, *J* = 21.5 Hz, *C10*), 84.9 (*C6*), 76.2 (*C12*), 66.4 (*C1*), 64.8 (*C7a*), 56.6 (*C7*), 52.0 (*C5*), 23.9 (*C13*). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.7 (s, CF_3), -114.4 (m, CF). HRMS (ESI): m/z calcd. for $[C_{22}H_{19}FNO_3]^+$ 478.1248, found 478.1245 $[M+H]^+$. For numeration of atoms see Scheme 8.

(+)-(6*S*,7*R*,7a*S*,12*R*)-**1'** (obtained from (−)-(6*S*,7*R*,7a*S*)-**17**): colorless oil, $[\alpha]_D$ = +30 (c = 0.5, EtOAc, 25 °C). HPLC analysis: ee 96 % (RT 22.3 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/i-PrOH = 98:2; temperature 40 °C; flow rate 1 ml/min).

(−)-(6*R*,7*S*,7a*R*,12*S*)-**1'** (obtained from (+)-(6*R*,7*S*,7a*R*)-**17**): colorless oil. HPLC analysis: ee > 99 % (RT 20.4 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/i-PrOH = 98:2; temperature 40 °C; flow rate 1 ml/min).

rac-**1'** (obtained from *rac*-**17**): colorless crystals. mp = 88 − 95 °C (MeOH). Sample for single crystal X-Ray analysis was obtained by crystallization from MeOH. CCDC 1987343 contains the supplementary crystallographic information for *rac*-**1'**.

Supporting information

Copies of NMR, FT-IR, HPLC chromatograms for all compounds. Crystallographic data for products *rac*-**1'** and *rac*-**9**. Molecular docking of antagonist **1** and its stereoisomers into the binding site of hNK_1 receptor. The Supporting Information is available free of charge on the ACS Publications website at DOI:

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difference in the predicted binding modes of **1** and **1'** may result in a noticeable difference in the hNK1 binding activity of these compounds (for detailed discussion of docking see Supporting information).

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