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Enantiomerically Pure and Highly Substituted Alicyclic α,α-Difluoro Ketones: Potential Inhibitors for Malarial Aspartic Proteases, the Plasmepsins

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The design and synthesis of novel fluorinated building blocks is of major interest in the development of new pharmaceuticals and agrochemicals. A quantitative search in the Protein Data Bank (PDB) manifests the use of di- and trifluoro hydrates for binding to hydrophilic enzyme active sites. Hydrated alicyclic α,α-difluorinated ketones attract attention since they provide suitable functionalities for binding to the pair of catalytically active aspartate (Asp) side chains at the active site of aspartic proteases. This article expands the synthetic availability of this novel class of binding elements. Enantiomerically pure alicyclic α,α-difluoro ketones are efficiently accessed by a straightforward route involving the separation of diastereoisomeric Mosher esters. The transformation into Mosher esters also enables the determination of the absolute configuration of the enantiomeric α,α-difluoro ketones. The synthetic protocol was further expanded to the preparation of highly substituted cyclohexyl-based α,α-difluoro ketones bearing two exit vectors to fill the corresponding side pockets in the malarial aspartic proteases, the plasmepsins. Moderate biological activities toward these enzymes were determined, with IC_{50} (median inhibitory concentration) values in the lower micromolar range.

Introduction

The development of novel building blocks for medicinal chemistry is a challenging and urgent target in research. In a recent study, it was shown that out of 800,000 frameworks registered by the Chemical Abstract Service (CAS), half can be assigned to only 143 different scaffolds.[1] This demonstrates the narrow focus of scientists on only a limited number of building blocks. A search in the commercially available Comprehensive Medicinal Chemistry (CMC) database for drugs shows a similar trend. A total of 50% of 5120 drugs can be described by only 32 of the most common fragments.[2] This lack of diversity has previously been recognized as a limitation in the drug discovery process.[3] The recent studies and applications of oxetanes show the high demand for new building blocks and are a striking representative of how successful such a task can be.[4–6] Building blocks bearing fluorine are potential contributors to this field of research, since the number of fluorinated pharmaceuticals and agrochemicals has dramatically increased over the last 50 years. Fluorinated molecules are of special interest, because the profits gained by the introduction of fluorine into a drug are way beyond the common known enhancements in metabolic stability.[7]

Recently, we reported that alicyclic α,α-difluorinated ketones can act as recognition elements for the two catalytic Asp side chains at the active site of the malarial aspartic proteases PM II and PM IV.[8] In a biological environment, the carbonyl function of these cyclic α,α-difluoro ketones is hydrated nearly to completion, which was demonstrated in a ^{19}F NMR study. Open-chain, peptidomimetic α,α-difluoro ketones are well known in medicinal chemistry. They have been used as inhibitors for serine proteases (human leucocyte elastase),[9] transferases (*N*-myristoyltransferase),[10] metalloproteases (matrix metalloprotease 13),[11] and, especially, aspartic proteases (renin[12,13] and HIV-1 protease[14,15]). A search in the Protein Data Bank (PDB) with the program Relibase+[16] revealed nine co-crystal structures for acyclic hydrated α,α-difluoro ketones as ligands. Eight fluorinated hydrates are involved in aspartic protease recognition,[17–22] and one is found in phosphoenolpyruvate mutase/isocitrate lyase.[23] The hydroxy groups of 2,2-difluoro-3,3-dihydroxybutanedioic acid ("hydrated 3,3-difluorooxalacetate") in the co-crystal structure of phosphoenolpyruvate mutase/isocitrate lyase form hydrogen bonds with Tyr, Asp, and Arg side chains, while also coordinating to an Mn^{II} ion, revealing a strong preference for hydrates as binding motifs for hydrophilic pockets. In seven of the eight co-structures of aspartic proteases, the hydrated α,α-difluoro ketones bind in a similar fashion, with both hydroxy groups interacting with the catalytic Asp

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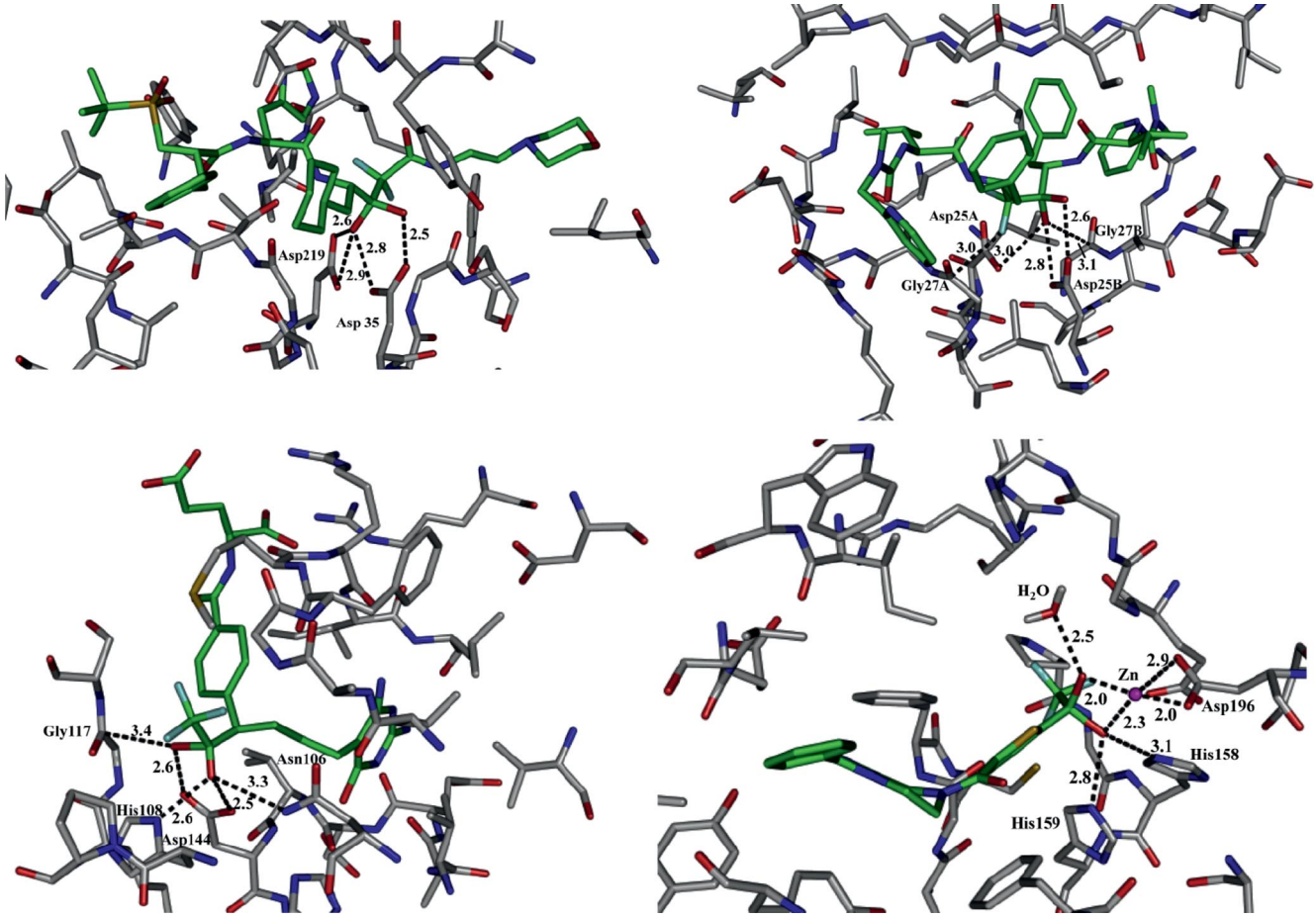


Figure 1. Top left: Co-crystal structure of a peptidomimetic α,α-difluoro ketone bound to the aspartic protease endothiapepsin (PDB code: 2JJJ). Top right: Co-crystal structure of a peptidomimetic α,α-difluoro ketone bound to HIV-1 aspartic protease (PDB code: 1DIF). Bottom left: The α,α,α-trifluoro ketone based inhibitor binds to the highly hydrophilic binding pocket of human GAR Tfase (PDB code: 1NJS). Bottom right: The α,α,α-trifluoro ketone based inhibitor in a co-crystal structure with the HDAC4 catalytic domain (PDB code: 2VQQ). Graphics were created with PyMOL. Color code: C skeleton of inhibitors: green, C atoms of protein: gray, O atoms: red, N atoms: blue, S atoms: yellow, F atoms: cyan, Zn atom: magenta.

dyad, while both fluorine atoms point into the bulk solvent.[17–21] A representative example is the endothiapepsin inhibitor shown in Figure 1 (top left). In the remaining case, a different binding pattern is found for the hydrated α,α-difluoro ketone bound to HIV-1 protease [Figure 1 (top right)].[22] Here, the hydroxy groups also interact with the Asp dyad, but in addition, one fluorine atom and one oxygen atom of the difluoro hydrate point towards the backbone carbonyl carbon atoms of neighboring Gly residues, thereby engaging in favorable orthogonal dipolar interactions.[24]

To further highlight the importance of α-fluorinated hydrates as binding elements, the PDB search was extended to hydrated α,α,α-trifluoro ketones. Twelve different co-crystal structures were found,[25–30] one of which involves a serine protease (chymotrypsin),[27] one a lyase (hydroxynitrile lyase),[29] one a cholinesterase (acetylcholinesterase),[26] three a histone deacetylase,[25] and seven the human glycinamide ribonucleotide transformylase (GAR Tfase).[28,30] In the co-crystal structure of chymotrypsin, two α,α,α-trifluoro ketones interact differently with the enzyme. One of the α,α,α-trifluoro ketones binds covalently to the Ser hydroxy group of the catalytic triad, while the second one occupies a site formed by Asp and Gln side chains and interacts in a similar mode to the one shown in Figure 1 (top left). Generally, hydrated α,α,α-trifluoro ketones have a strong preference for hydrophilic enzyme pockets. Hydrated α,α,α,α′,α′,α′-hexafluoroacetone in the hydroxy nitrile lyase forms hydrogen bonds with a water molecule, a Thr side chain, and the backbone carbonyl group of an Ile residue. The hydrated α,α,α-trifluoro ketone in the acetylcholinesterase complex forms hydrogen bonds with a His side chain and two backbone NH groups. In the humane GAR Tfase, the hydrate undergoes hydrogen bonding with His, Asp, and Glu side chains, while one hydrate oxygen atom engages in an orthogonal dipolar interaction with a backbone carbonyl group [Figure 1 (bottom left)]. This binding pattern is found for all seven co-crystal structures of human GAR Tfase and its corresponding α,α,α-trifluoride-based ligands. In the histone deacetylase, the hydrate binds to

Zn^{II}, water, and His and Asp side chains [Figure 1 (bottom right)]. This binding pattern is conserved in all three reported examples.

The fact that 300–660 million people are annually infected with malaria reveals the strong demand for new therapies, especially since the parasite *Plasmodium falciparum* developed resistance against the common malaria drugs.[31–33] The aspartic proteases, plasmepsins (PM) I, II, and IV, as well as the structurally related histo-aspartic protease (HAP), which participate in the hemoglobin degradation process in the food vacuole of the parasite during the erythrocytic stage of its life cycle, seem to be promising targets.[34–36] These enzymes have been successfully inhibited by a variety of ligands as revealed both in target- and cell-based assays.[37–42] The majority of non-peptidic ligands addresses the catalytic Asp dyad, a lipophilic "merged" S1/S3 pocket, and a so-called "flap-open" pocket, which is induced through ligand binding.

Here, we report the synthesis of the first enantiomerically pure alicyclic α,α-difluoro ketones (*S*)-**1** and (*R*)-**1**, which are hydrated nearly to completion in aqueous solutions[8] and present promising new building blocks to address catalytic dyads in aspartic proteases and, if suitably decorated, other hydrophilic enzyme active sites.

Results and Discussion

Synthesis of Enantiomerically Pure α,α-Difluoro Ketones

We had earlier reported the synthesis and binding affinity to the plasmepsin enzymes of racemic hydrated α,α-difluoro ketone (±)-**2** and its hydroxylated precursors (±)-**3** and (±)-**4**,[8] and it was of interest to prepare representatives of these novel building blocks in optically pure form (Figure 2). Compared to the earlier racemic compounds, the target molecules (*S*)-**1** and (*R*)-**1** in this study, designed using the modeling software MOLOC,[43] bear a cyclopentylethyl instead of an *n*-pentyl chain to fill the "flap-open" pocket. In earlier work, we had seen a significant increase in binding affinity for ligands bearing a terminal cyclopentyl moiety on the substituent to fill this pocket [cf. compare (±)-**5** and (±)-**6** in Figure 2].[38] The naphthylethyl substituent to fill the spacious lipophilic "S1/S3 pocket" was maintained in the new ligands.

Racemic α,α-difluoro ketone (±)-**1** was synthesized starting from 4-iodoaniline (**7**) and the previously described difluorides (±)-**8** and (±)-**9**[8] (Scheme 1). 4-Iodoaniline (**7**) was cross-coupled in a Sonogashira reaction ([$PdCl_2(PPh_3)_2$], CuI, Et_3N) with cyclopentylacetylene (**10**) to yield alkyne **11**, which was subsequently hydrogenated (PtO_2/C, H_2) to aniline **12**. Coupling of amine **12** with acyl chloride **13**[8] (Et_3N) to amide **14** was followed by reduction (BH_3·THF) to afford aniline **15**. The difluorinated building blocks (±)-**8** or (±)-**9** were coupled (DIPEA; for abbreviations, see scheme captions) with aniline **15** to yield amides (±)-**16** and (±)-**17**, respectively. Saponification (NaOMe) of (±)-**16** and (±)-**17** afforded alcohols (±)-**18** and (±)-**19**, respectively. The former was oxidized (Dess–Martin periodinane) to difluoro ketone (±)-**1**. After oxidation and standard aqueous workup, a mixture of ketone (±)-**1** and its corresponding hydrate was obtained. This mixture was stirred in the presence of molecular sieves (4 Å) to yield pure ketone (±)-**1**.

The enantiomerically pure difluoro ketones (–)-**1** and (+)-**1** were synthesized starting from alcohols (±)-**18** and (±)-**19** (Scheme 2). The racemic mixtures (±)-**18** and (±)-**19** were transformed (Mosher's acid chloride, Et_3N, DMAP) into their diastereoisomeric *trans*-Mosher esters (–)-**20** and (–)-**21**, and *cis*-Mosher esters (+)-**22** and (–)-**23**, respectively. The resulting mixtures of the *trans* diastereoisomers (–)-**20** and (–)-**21** and the *cis* diastereoisomers (+)-**22** and (–)-**23**, respectively, were individually separated by HPLC on an achiral phase (Hibar, Si60; see Supporting Information). Individual saponification (NaOMe) of (–)-**20**,

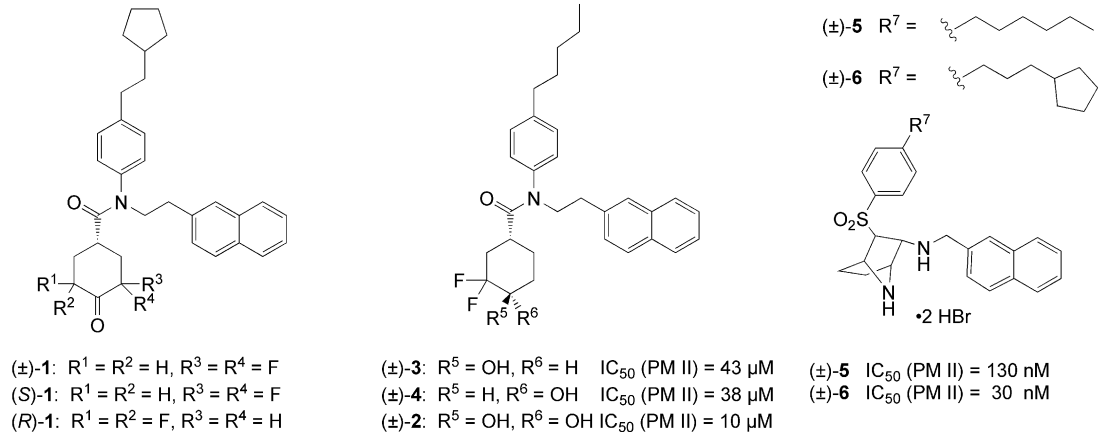
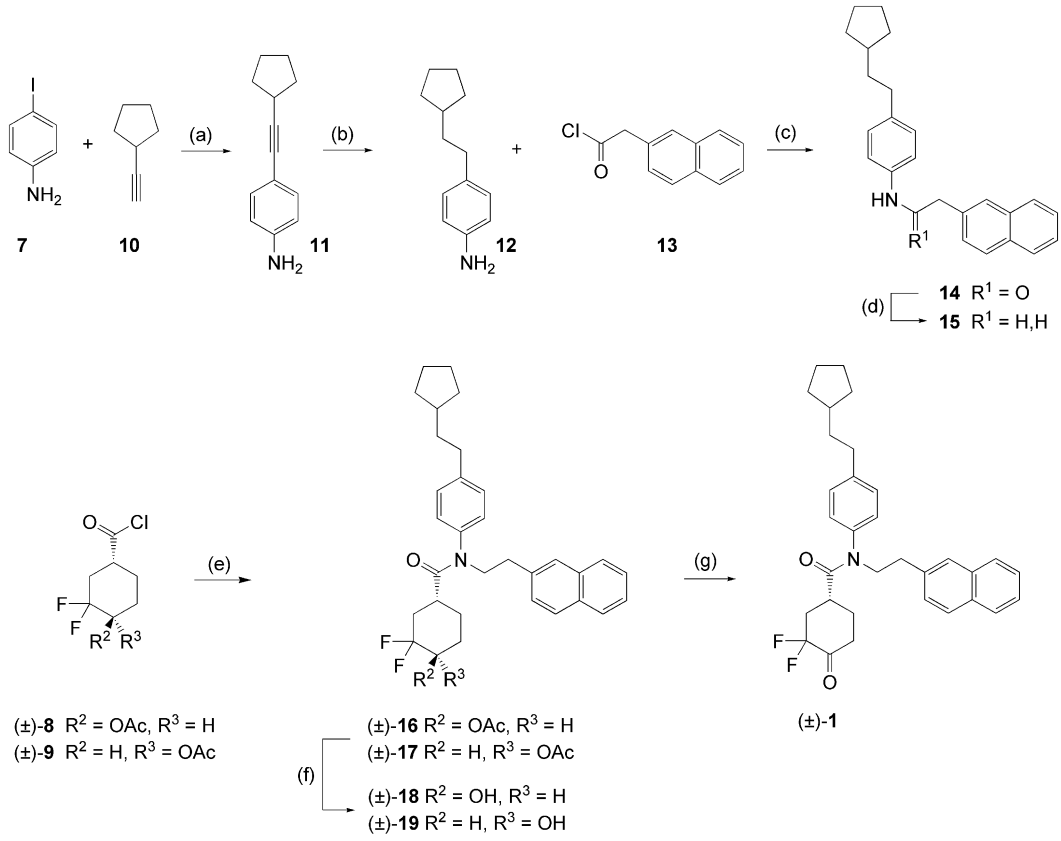
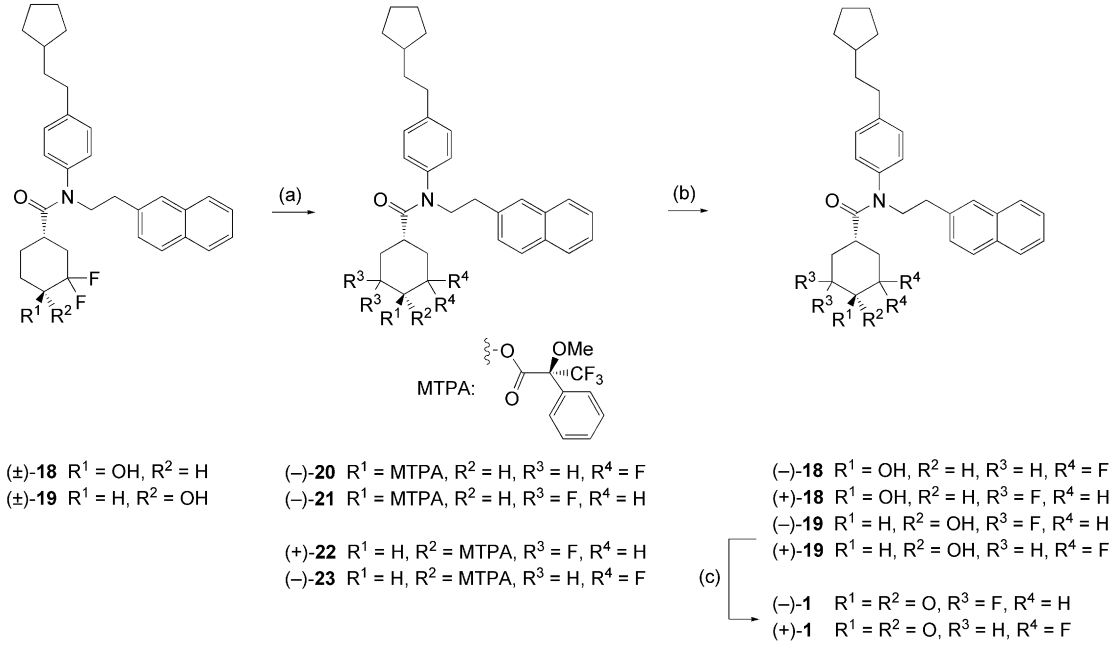


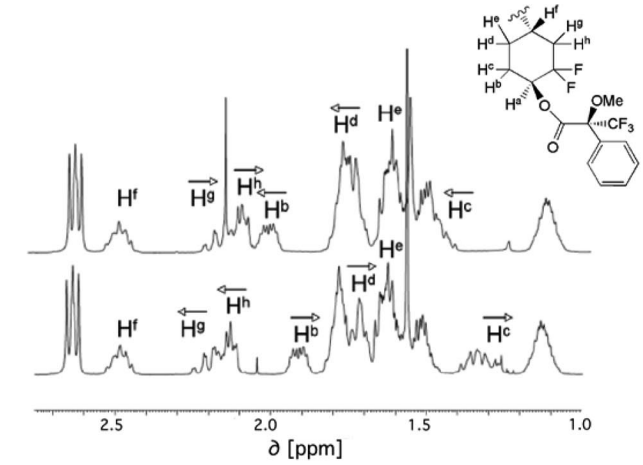
Figure 2. Left: Racemic and enantiopure α,α-difluoro ketones (±)-**1**, (*S*)-**1**, and (*R*)-**1** with a cyclopentylethyl moiety as a binding motif for the "flap-open" pocket. Middle: The racemic hydrated α,α-difluoro ketone (±)-**2** and its hydroxy precursors (±)-**3** and (±)-**4** were proven to be inhibitors for the malarial aspartic protease PM II.[8] Right: Based on the biological results obtained previously for the cyclic amines (±)-**5** and (±)-**6**,[38] a cyclopentylethyl residue was selected in (*S*)- and (*R*)-**1** to occupy the "flap-open" pocket. For ligands with the new difluorohydrate "needle", modeling with MOLOC suggested the cyclopentylethyl to be more appropriate than the cyclopentylpropyl residue used in the amine ligands.



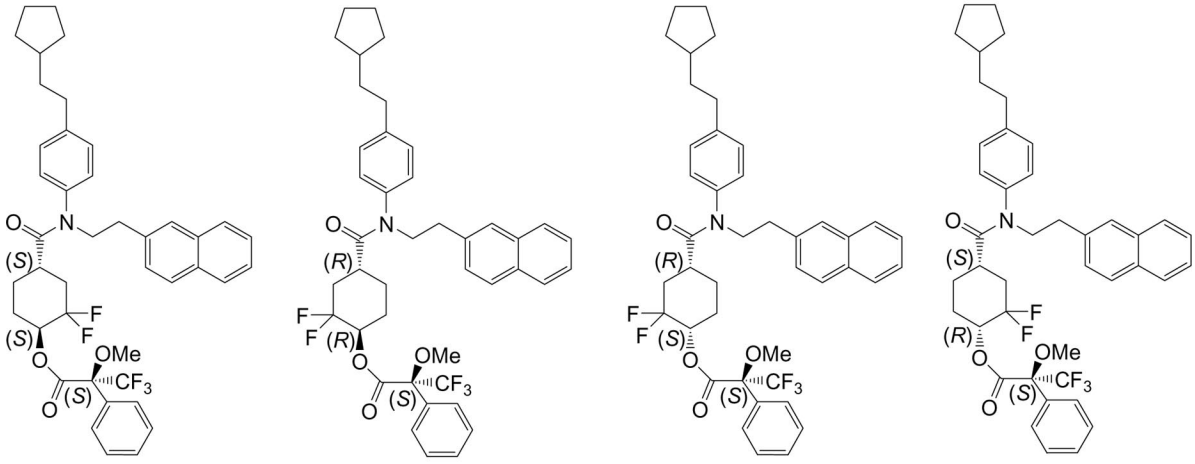
Scheme 1. (a) $[PdCl_2(PPh_3)_2]$, CuI, Et_3N, CH_2Cl_2, reflux, 48 h. (b) PtO_2/C, H_2, EtOH, 22 °C, 16 h; 64% (over two steps). (c) Et_3N, THF, 22 °C, 16 h; 70%. (d) BH_3·THF, reflux, 3 h; 92%. (e) **15**, DIPEA, CH_2Cl_2, 22 °C, 16 h; 94% [(±)-**16**], 90% [(±)-**17**]. (f) NaOMe, THF, MeOH, 22 °C, 3 h; 93% [(±)-**18**], 91% [(±)-**19**]. (g) Dess–Martin periodinane, CH_2Cl_2, 22 °C, 3 h; 70%. DIPEA = diisopropylethylamine.



Scheme 2. (a) (*R*)-(–)-Mosher's acid chloride, DMAP, THF, 22 °C, 12 h; 43% [(–)-**20**], 43% [(–)-**21**], 46% [(+)-**22**], 46% [(–)-**23**]. (b) NaOMe, THF, MeOH, 22 °C, 3 h; 90% [(–)-**18**], 83% [(+)-**18**], 90% [(–)-**19**], 90% [(+)-**19**]. (c) Dess–Martin periodinane, CH_2Cl_2, 22 °C, 3 h; 67% [(–)-**1**], 77% [(+)-**1**]. DMAP = 4-(*N*,*N*-dimethylamino)pyridine. MTPA = α-methoxy-α-(trifluoromethyl)phenylacetic acid.



	(–)-**20**	(–)-**21**
H^a	5.16	5.18
H^b	1.92	2.04
H^c	1.31	1.46
H^d	1.71	downfield
H^e	–	–
H^f	2.49	2.50
H^g	2.14	2.12
H^h	2.22	2.20
F	–102.83	–103.66
F	–115.92	–116.35



(–)-**20** (–)-**21** (+)-**22** (–)-**23**

Figure 3. Top left: An overlay of the ^{1}H NMR (400 MHz, 300 K) spectra (aliphatic range) of the *trans*-esters (–)-**20** and (–)-**21** clearly reveals the differences in chemical shift for corresponding resonances. Table top right: Chemical shifts for the relevant protons or fluorine atoms in the NMR spectra of (–)-**20** and (–)-**21**. Bottom: the absolute configuration was assigned for (–)-**20**, (–)-**21**, (+)-**22**, and (+)-**23** based on the chemical shift differences seen in the ^{1}H and ^{19}F NMR spectra.

(–)-**21**, (+)-**22**, and (–)-**23** yielded the enantiomerically pure alcohols (–)-**18**, (+)-**18**, (–)-**19**, and (+)-**19**, respectively. Oxidation of the *trans*-alcohols (Dess–Martin periodinane) gave the enantiomerically pure difluoro ketones (*R*)-(–)-**1** and (*S*)-(+)-**1**. Their absolute configurational assignment is presented in the following section.

Derivatization of the difluoroalcohols (±)-**18** and (±)-**19** via the Mosher esters not only served to produce enantiomerically pure inhibitors, but also allowed the determination of the absolute configuration by the well-established Mosher ester method.[44] In the most stable conformation, the CF_3 group and the carbonyl function of the ester are eclipsed. Resonances in the ^{1}H and ^{19}F NMR spectra, which are influenced by the OMe moiety of the MTPA ester should shift downfield, and signals, which are influenced by the MTPA phenyl group, should shift upfield. To avoid mistakes in the determination of the absolute configuration, this must be true for all influenced protons or fluorine atoms.[45] The ^{1}H NMR spectra of the *trans*-Mosher esters (–)-**20** and (–)-**21** were recorded and compared with each other (Figure 3). The observed chemical shifts allowed an unambiguous configurational assignment. For (–)-**20**, signals of H^b to H^d are all shifted more upfield in comparison with those of (–)-**21**; the H^e signal could not be detected since it overlaps with the alkyl chain resonances of (–)-**20** or (–)-**21**. In comparison, the signals of H^g, H^h, and one of the two fluorine atoms of (–)-**20** are shifted downfield in comparison to those of (–)-**21** (Figure 3). In the same way, the ^{1}H and ^{19}F NMR spectra of the *cis*-esters (+)-**22** and (–)-**23** were analyzed (see Supporting Information). Therefore, the absolute configuration was assigned for the *trans*- and *cis*-esters as shown in Figure 3.

Highly Substituted Cyclohexyl-Based α,α-Difluoro Ketones

To prepare new inhibitors with a furanyl residue to occupy the "S1/S3 pocket" and to further illustrate the syn-

thetic accessibility of highly decorated α,α-difluoro ketones and their hydrates, inhibitor (±)-**24** with two exit vectors was prepared by a route involving alcohol (±)-**25** as the key precursor and as another potential ligand (Figure 4).

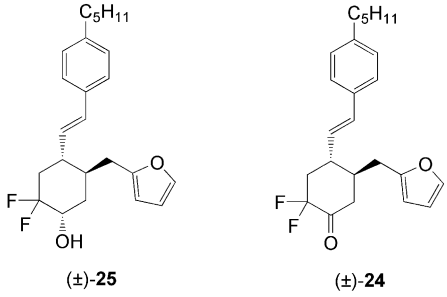


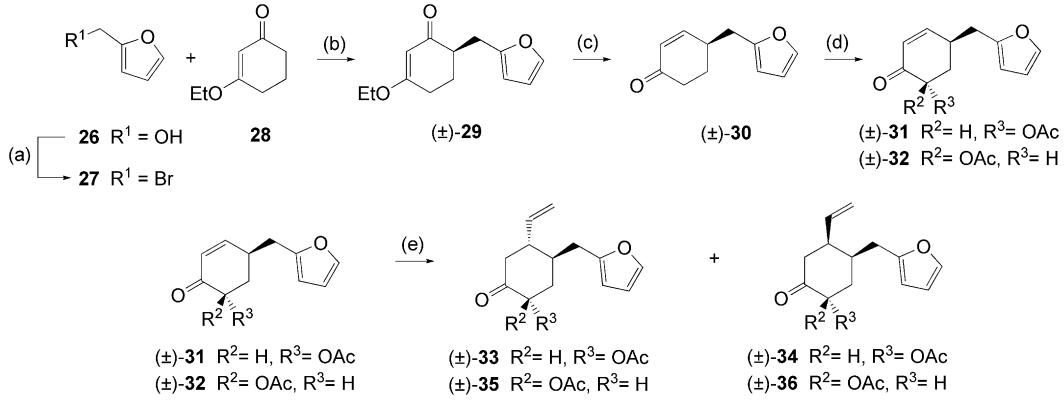
Figure 4. The potential PM inhibitors (±)-**24** and (±)-**25** with a highly decorated cyclohexane moiety.

The synthesis started from the commercially available furfuryl alcohol (**26**) (Scheme 3), which was brominated (PBr_3) to give bromide **27**. The latter polymerized upon concentration and therefore had to be used directly as a solution in THF. Cyclohexenone **28** was alkylated (LDA, HMPA) with bromide **27** to yield ketone (±)-**29**, which was transformed under reductive conditions (DIBAL-H), followed by acid-mediated cleavage of the enol ether (*p*TsOH), into cyclohexenone (±)-**30**. In a Rubottom reaction, cyclohexenone (±)-**30** was oxidized (TMSCl, *m*-CPBA, $Et_3N{\cdot}HF$, Ac_2O) to give the α-acetoxy ketones (±)-**31** and (±)-**32**.[46] The observed diastereoisomeric ratio of (±)-**31**/(±)-**32** was 4:1, which shows a moderate steric influence of the furanyl group in this reaction. The constitution and the relative configuration of (±)-**31** and (±)-**32** were proven by $^1H,^1H$-COSY and 1D-NOE NMR methods (see Supporting Information). Michael addition (CuI, vinylmagnesium bromide) to ketone (±)-**31** gave the two diastereoisomeric α-acetoxy ketones (±)-**33** and (±)-**34**. In the same way, ketone (±)-**32** was transformed into diastereoisomers (±)-**35** and (±)-**36**. Both pairs of diastereoisomeric acetates, (±)-**33**/(±)-**34** and (±)-**35**/(±)-**36**, were obtained in a ratio of 2.5:1. This indicates that the stereoselectivity in the Michael addition is mainly due to the furanyl substituent and not to the acetyl group. The constitution and the relative configuration of (±)-**34** to (±)-**36** were proven by $^1H,^1H$-COSY and 1D-NOE NMR methods (see Supporting Information).

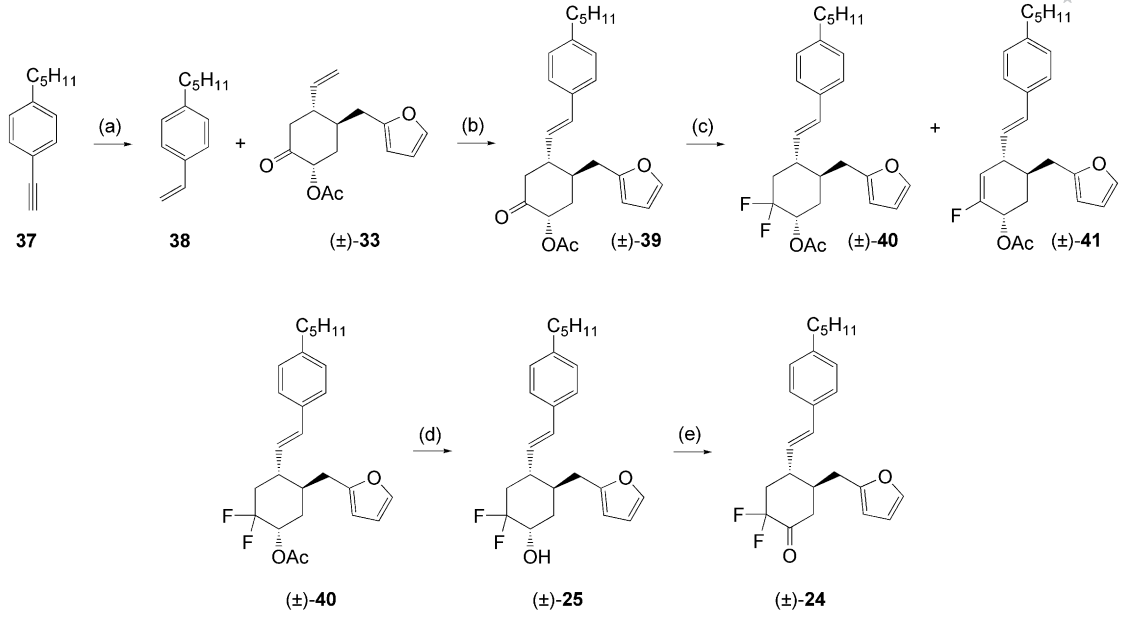
α,α-Difluoro ketone (±)-**24** was finally synthesized by starting from precursor (±)-**33** and alkyne **37** (Scheme 4). The commercially available 1-ethynyl-4-pentylbenzene (**37**) was hydroborated (9-BBN, acetic acid) to give alkene **38**. In a cross-metathesis reaction (Grubbs-2 catalyst), alkene **38** was coupled with (±)-**33** to the trisubstituted cyclohexanone (±)-**39**. The keto function of (±)-**39** was difluorinated (DAST) to yield difluoro ketone (±)-**40** and fluoro(vinyl)-cyclohexene (±)-**41** as an elimination side product. Subsequent saponification (aqueous K_2CO_3) of (±)-**40** to alcohol (±)-**25**, followed by oxidation (Dess–Martin periodinane), yielded α,α-difluoro ketone (±)-**24**.

Biological Results

The biological activity of the prepared compounds towards the PMs (Figure 5, and table in Figure 5) was measured in a fluorescence resonance energy transfer (FRET) assay (see Exp. Sect.). For all measured compounds, no activity was seen for PM II and PM IV in the range of the assay (cut off at 100 μM) except for (±)-**1** [median inhibitory concentration IC_{50}(PM IV) = 72 μM] and (±)-**24** [IC_{50}(PM II) = 67 μM]. The enantiomerically pure, hydroxy-based precursors (–)-**18** and (–)-**19** show a low activity towards PM I. The racemic difluoro ketone (±)-**1** and its enantiomerically pure analogues (+)-**1** and (–)-**1** have a low double-digit micromolar activity towards PM I. In comparison with their alcohol precursors, their activity is higher, which is in accordance with observations made ear-

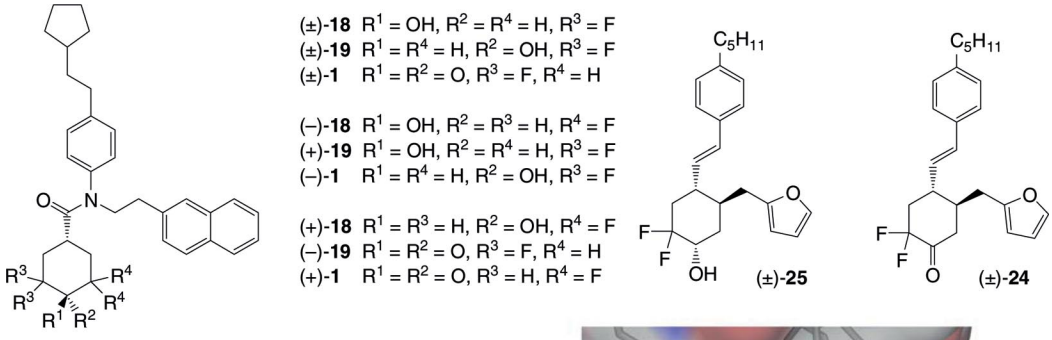


Scheme 3. (a) PBr_3, pyridine, Et_2O, –30 °C, 5 h. (b) DIPA, *n*BuLi, HMPA, THF, 0 °C to –78 °C, 3 h; 62% (over two steps). (c) 1. DIBAL-H, Et_2O, 0 °C, 4 h; 2. *p*TsOH, Et_2O, 22 °C, 2 h; 78%. (d) 1. DIPA, *n*BuLi, TMSCl, hexane, –20 °C to 0 °C, 2 h; 2. *m*-CPBA, hexane, 22 °C, 1 h; 3. $Et_3N{\cdot}HF$, Ac_2O, Et_3N, 22 °C, 1 h; 36% [(±)-**31**], 9% [(±)-**32**]. (e) CuI, vinylmagnesium bromide, TMEDA, TMSCl, THF, –78 °C, 3 h; 48% [(±)-**33**], 19% [(±)-**34**]; 46% [(±)-**35**], 17% [(±)-**36**]. DIPA = diisopropylamine, HMPA = hexamethylphosphoramide, DIBAlH = diisobutylaluminium hydride, Ts = tosyl, TMS = trimethylsilyl, *m*-CPBA = *meta*-chloroperbenzoic acid, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.



Scheme 4. (a) 1. 9-BBN, THF, 22 °C, 5 h; 2. acetic acid, 22 °C, 2 h; 64%. (b) Grubbs-2 catalyst, CH_2Cl_2, reflux, 6 h; 25%. (c) DAST, CH_2Cl_2, reflux, 4 h; 36% [(±)-**40**], 36% [(±)-**41**]. (d) K_2CO_3, MeOH, H_2O, CH_2Cl_2, 22 °C, 4 h; 54%. (e) Dess–Martin periodinane, CH_2Cl_2, 22 °C; 86%. DAST = (diethylamino)sulfur trifluoride.

lier.[8] Nevertheless, an expected difference in the binding affinity of the racemic derivative (±)-**1** and its enantiomerically pure equivalents (+)-**1** and (–)-**1** was not observed.[47] Also, in the case of the highly decorated inhibitors, the keto derivative (±)-**24** is more active than its hydroxylated precursor (±)-**25**. Although the "S1/S3 pocket" is only targeted by a small furanyl substituent, inhibitor (±)-**24** has a promising activity for PM I in the low double-digit micromolar range. It is expected that further substitution of the furanyl ring, to ensure full space filling of the spacious "S1/S3 pocket", could yield activities in the nanomolar IC_{50} range.



Substance (IC_{50} in μM)	PM I	PM II	PM IV
(±)-**18**	>100	>100	>100
(±)-**19**	>100	>100	>100
(±)-**1**	17	>100	72
(–)-**18**	97	>100	>100
(+)-**19**	>100	>100	>100
(–)-**1**	46	>100	>100
(+)-**18**	>100	>100	>100
(–)-**19**	37	>100	>100
(+)-**1**	25	>100	>100
(±)-**25**	>100	>100	>100
(±)-**24**	38	67	>100

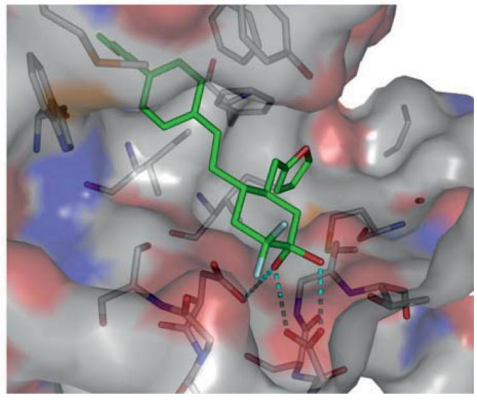


Figure 5. The biological activities of the amide-based and the bidentate inhibitors towards the PMs. Bottom right: the proposed binding geometry for the (*R*,*S*) enantiomer of **24**, modeled into PM II (PDB code: 2IGX) with the program MOLOC.[43]

Conclusions

Hydrated alicyclic α,α-difluoro ketones represent novel fluorinated building blocks for binding to hydrophilic active sites in enzymes. A comprehensive search in the PDB uncovers a variety of possible targets for these "needles", way beyond the malarial aspartic proteases, the plasmepsins, that are of interest in this work. We report synthetic protocols providing broad accessibility towards alicyclic α,α-difluoro ketones in enantiomerically pure form or as highly decorated derivatives. A late-stage transformation of alicyclic, α,α-difluoro hydroxy based precursors into Mosher esters and the subsequent separation of the formed diastereoisomers ultimately enables straightforward access to enantiomerically pure alicyclic α,α-difluoro ketones. The Mosher ester procotol also provides a reliable procedure to determine their absolute configuration. Finally, the moderate biological activity towards PM I suggests that hydrated alicyclic α,α-difluoro ketones are suitable "needles" to address the catalytic Asp dyad of aspartic proteases. Appropriate decoration should also turn them into promising building blocks for binding to hydrophilic sites of other target enzymes.

Experimental Section

General: Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. THF was freshly distilled from sodium benzophenone, CH_2Cl_2 from CaH_2 and toluene from sodium. Unless mentioned otherwise, all products were dried under high vacuum (10^{-2} Torr) before analytical characterization. Column chromatography (CC) was conducted on silica gel (230–400 mesh, 0.040–0.063 mm) from Fluka. HPLC performed with a Merck-Hitachi system (Model D-7000, Chromatography Data Station Software, Version 4.1, P/N: 810-8652-01) with a Merck Hibar Si60 column; the system was equipped with an L-7150 pump, an L-7200 autosampler, and an L-7400 UV detector. Analytical thin layer chromatography (TLC) was conducted on silica gel 60-$F_{254\,nm}$ (on glass, Merck). Plates were visualized by UV light at 245 nm or staining with a solution of $KMnO_4$ (1.5 g), K_2CO_3 (10 g), 5% NaOH (2.5 mL) in H_2O (150 mL). Melting points (m.p.) were determined with a Büchi-510 apparatus and are uncorrected. IR: Perkin–Elmer Spectrum BX FTIR System spectrometer (ATR unit, Attenuated Total Reflection, Golden Gate). NMR (^1H, ^{13}C, ^{19}F, ^1H,^1H COSY): Varian Gemini-300, Bruker AV-400 and DRX-400; spectra were recorded at 25 °C using the solvent peak as an internal reference. Coupling constants (*J*) are given in Hz. The resonance multiplicities are described as s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). The exchangeable OH signals are not always observed in the ^1H NMR spectra. Mass spectra were recorded with a Varian-IonSpec-MALDI-FT-ICR (MALDI, with 2,5-dihydroxybenzoic acid as the matrix), a Waters-Micromass-AutoSpec-Ultima (EI, 70 eV) and a Varian IonSpec ESI-FT-ICR. If the molecular ion [M^+] is the parent peak, only its *m*/*z* value is reported. If a fragment is the parent peak, the relative intensity of the molecular ion, as well as the fragment with 100% intensity are given. For MALDI spectra, the [M + H]$^+$, [M + Na]$^+$ and [M + K]$^+$ peaks are reported if they occur in the spectra. Elemental analyses (EA) were measured in the Mikrolabor of the Laboratorium für Organische Chemie. The nomenclature was generated with the computer program ACD Name (ACD/Labs).

FRET Assay for the Determination of IC_{50} Values:[42] The proteolytic activity of the particular enzyme was tested in a FRET assay. M-2120 from Bachem was used as the substrate. The enzyme, with an approximative concentration of 1 nM, was incubated with the substrate (concentration ca. 1 μM) at 37 °C in the presence of a sodium acetate solution (50 mM), at pH = 5, 12.5% (v/v) glycerol, 0.1% (v/v) bovine serum albumin, and 10% $(CH_3)_2SO$. The enzyme activity was determined from the rate of conversion of the substrate by plotting the corresponding signal of increasing fluorescence emission. The fluorescence was analyzed with a FluoroStar Galaxy instrument from BMG, and the excitation and emission filters 355 and 520 nm, respectively, were used. The test compounds were dissolved in the above described solution and, if necessary, diluted with 100% $(CH_3)_2SO$. The biological activity is expressed by the IC_{50} value.

Molecular Modeling: Potential inhibitors were manually docked within the known structure of PM II, co-crystallized in complex with an inhibitor based on a piperidinium "needle" and with a "flap-open" pocket (PDB code: 2IGX).[41] The enzyme structure without the piperidinium ligand was fixed and the energy of the system minimized by using the MAB force field as implemented in the computer program MOLOC.[43] Evaluation of different binding conformations of the inhibitors was based on (i) avoidance of unfavorable steric contacts, (ii) formation of favorable hydrogen-bonding contacts, and (iii) optimal filling of the space within binding pockets by establishing the maximal number of attractive van der Waals contacts between enzyme and ligand. For the chiral inhibitors (±)-**1**–**4** and their corresponding precursors, the (*R*) enantiomer fits best into the active site, according to the modeling. For comparative reasons, all modeling was also performed by starting from two similar co-crystal structures (PDB code: 2IGY[41] and 2BJU[42]), following the same procedure as described.

(1*RS*,4*RS*)-4-({[4-(2-Cyclopentylethyl)phenyl][2-(2-naphthyl)ethyl]-amino}carbonyl)-2,2-difluorocyclohexyl Acetate [(±)-16]: To a solution of acyl chloride (±)-**8**[8] (250 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) under Ar at 22 °C, amine **15** (297 mg, 0.86 mmol) and DIPEA (327 μL, 242 mg, 1.9 mmol) were added. The mixture was stirred at 22 °C for 16 h and subsequently treated with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by CC (SiO_2; EtOAc/pentane, 2:98) yielded (±)-**16** as a colorless wax (538 mg, 94%). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.13–1.20 (m, 2 H), 1.31–1.36 (m, 1 H), 1.51–1.60 (m, 2 H), 1.61–1.69 (m, 5 H), 1.70–1.72 (m, 2 H), 1.78–1.86 (m, 3 H), 1.92–1.97 (m, 1 H), 2.05–2.18 (m, 1 H), 2.08 (s, 3 H), 2.48–2.54 (m, 1 H), 2.67 (t, *J* = 8.0 Hz, 2 H), 3.00–3.07 (m, 2 H), 3.94–4.04 (m, 2 H), 4.90–4.98 (m, 1 H), 6.95, 7.21 (*J* = 8.2 Hz, 4 H, AA′BB′), 7.32 (dd, *J* = 1.7, 8.4 Hz, 1 H), 7.42–7.47 (m, 2 H), 7.62 (s, 1 H), 7.74–7.77 (m, 2 H), 7.79–7.82 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.84, 25.26, 26.66, 27.48 (d, *J* = 5.9 Hz), 32.72, 34.09, 34.78, 36.30 (t, *J* = 23.0 Hz), 37.68 (d, *J* = 9.2 Hz), 37.88, 39.83, 50.99, 71.14 (t, *J* = 19.9 Hz), 120.21 (dd, *J* = 244.3, 247.9 Hz), 125.43, 126.05, 127.18, 127.37, 127.45, 127.63, 127.64, 128.04, 129.84, 132.23, 133.56, 136.12, 139.43, 143.63, 169.91, 172.72 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –116.79 (d, *J* = 238.9 Hz, 1 F), –104.22 (d, *J* = 238.7 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 2943, 2864, 1740, 1652, 1606, 1510, 1409, 1368, 1306, 1231, 1178, 1096, 1061, 955, 910, 856, 818, 731 cm^{-1}. MALDI-MS: *m*/*z* (%): calcd. for $C_{34}H_{40}F_2NO_3^+$ 548.2971; found 548.2972 (75, [M + H]$^+$); calcd. for

$C_{34}H_{39}F_2NO_3Na^+$ 570.2790; found 570.2787 (100, $[M + Na]^+$); calcd. for $C_{34}H_{39}F_2NO_3K^+$ 586.2530; found 586.2541 (70, $[M + K]^+$).

(1*SR*,4*RS*)-4-({[4-(2-Cyclopentylethyl)phenyl][2-(2-naphthyl)ethyl]-amino}carbonyl)-2,2-difluorocyclohexyl Acetate [(±)-17]: To a solution of acyl chloride (±)-**9**[8] (200 mg, 0.83 mmol) in CH_2Cl_2 (5 mL) under Ar at 22 °C, amine **15** (238 mg, 0.86 mmol) and DIPEA (261 μL, 194 mg, 1.5 mmol) were added. The mixture was stirred at 22 °C for 16 h and subsequently treated with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by CC (SiO_2; EtOAc/pentane, 2:98) yielded (±)-**17** as a colorless wax (411 mg, 90%). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.02–1.12 (m, 2 H), 1.32–1.43 (m, 2 H), 1.43–1.49 (m, 2 H), 1.52–1.61 (m, 4 H), 1.66–1.74 (m, 5 H), 1.76–1.89 (m, 1 H), 2.04 (s, 3 H), 2.19–2.36 (m, 1 H), 2.38–2.45 (m, 1 H), 2.58 (t, J = 8.0 Hz, 2 H), 2.97 (dt, J = 2.6, 7.6 Hz, 2 H), 3.90 (dt, J = 2.1, 7.9 Hz, 2 H), 4.88–4.94 (m, 1 H), 6.87, 7.13 (AA′BB′, J = 8.3 Hz, 4 H), 7.25 (dd, J = 1.7, 8.4 Hz, 1 H), 7.33–7.39 (m, 2 H), 7.55 (s, 1 H), 7.65–7.70 (m, 2 H), 7.71–7.74 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.00, 22.29, 25.26, 26.83 (d, J = 5.5 Hz), 32.56 (t, J = 23.2 Hz), 32.72, 34.14, 34.77, 37.58 (d, J = 9.5 Hz), 37.82, 39.81, 51.17, 68.22 (dd, J = 12.1, 39.5 Hz), 120.59 (dd, J = 237.8, 252.5 Hz), 125.43, 126.04, 127.19, 127.39, 127.45, 127.61, 127.65, 128.06, 129.84, 132.24, 133.57, 136.21, 139.53, 143.56, 169.50, 173.19 (d, J = 1.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.99 (d, J = 253.0 Hz, 1 F), –102.83 (d, J = 252.8 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 2940, 2862, 2360, 1753, 1652, 1603, 1510, 1438, 1408, 1368, 1318, 1228, 1100, 1029, 947, 855, 818, 743, 623 cm^{-1}. MALDI-MS: m/z (%): calcd. for $C_{34}H_{40}F_2NO_3^+$ 548.2971; found 548.2969 (100, $[M + H]^+$); calcd. for $C_{34}H_{39}F_2NO_3Na^+$ 570.2790; found 570.2788 (70, $[M + Na]^+$); calcd. for $C_{34}H_{39}F_2NO_3K^+$ 586.2530; found 586.2537 (25, $[M + K]^+$).

(1*RS*,4*RS*)-*N*-[4-(2-Cyclopentylethyl)phenyl]-3,3-difluoro-4-hydroxy-*N*-[2-(2-naphthyl)ethyl]cyclohexanecarboxamide [(±)-18]: To a solution of ester (±)-**16** (50 mg, 0.09 mmol) in THF/MeOH (2:3) (1.5 mL) under Ar at 0 °C, NaOMe (10 mg, 0.18 mmol) was added and the mixture stirred at 22 °C for 3 h. The solution was treated with saturated aqueous $NaHCO_3$ solution (2 mL) and the aqueous phase extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by CC (SiO_2; EtOAc/pentane, 3:7) yielded alcohol (±)-**18** as a colorless wax (43 mg, 93%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02–1.12 (m, 2 H), 1.13–1.20 (m, 1 H), 1.41–1.52 (m, 3 H), 1.53–1.60 (m, 5 H), 1.69–1.77 (m, 3 H), 1.85–1.91 (m, 1 H), 1.93–1.99 (m, 1 H), 2.00–2.04 (m, 1 H), 2.35–2.43 (m, 1 H), 2.58 (t, J = 8.0 Hz, 2 H), 2.95 (dt, J = 1.9, 7.8 Hz, 2 H), 3.58–3.68 (m, 1 H), 3.90 (dt, J = 3.6, 7.6 Hz, 2 H), 6.86, 7.13 (AA′BB′, J = 8.3 Hz, 4 H), 7.23 (dd, J = 1.7, 8.4 Hz, 1 H), 7.33–7.40 (m, 2 H), 7.53 (s, 1 H), 7.65–7.68 (m, 2 H), 7.71–7.73 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.25, 26.83, 30.03 (d, J = 6.5 Hz), 32.71, 34.09, 34.78, 35.70 (t, J = 23.3 Hz), 37.86, 37.90 (d, J = 7.7 Hz), 39.82, 50.99, 71.01 (t, J = 21.4 Hz), 121.68 (dd, J = 243.0, 245.2 Hz), 125.42, 126.03, 127.16, 127.37, 127.44, 127.59, 127.64, 128.03, 129.84, 132.22, 133.55, 136.14, 139.44, 143.61, 173.06 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –121.23 (d, J = 235.9 Hz, 1 F), –105.56 (d, J = 235.9 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3410, 2939, 2863, 1736, 1638, 1604, 1510, 1450, 1410, 1364, 1299, 1272, 1242, 1174, 1089, 1018, 996, 949, 854, 817, 743 622 cm^{-1}. MALDI-MS: m/z (%): calcd. for $C_{32}H_{38}F_2NO_2^+$ 506.2865; found 506.2869 (100, $[M + H]^+$); calcd. for $C_{32}H_{37}F_2NO_2Na^+$ 528.2685; found 528.2688 (52, $[M + Na]^+$); calcd. for $C_{32}H_{37}F_2NO_2K^+$ 544.2434; found 544.2424 (34, $[M + K]^+$).

(1*S*,4*R*)-*N*-[4-(2-Cyclopentylethyl)phenyl]-3,3-difluoro-4-hydroxy-*N*-[2-(2-naphthyl)ethyl]cyclohexanecarboxamide [(±)-19]: To a solution of ester (±)-**17** (50 mg, 0.09 mmol) in THF/MeOH (2:3) (1.5 mL) under Ar at 0 °C, NaOMe (10 mg, 0.18 mmol) was added and the mixture stirred at 22 °C for 3 h. The solution was treated with saturated aqueous $NaHCO_3$ solution (2 mL) and the aqueous phase extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by CC (SiO_2; EtOAc/pentane, 3:7) yielded alcohol (±)-**19** as a colorless wax (42 mg, 91%). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.11 (m, 2 H), 1.31–1.34 (m, 2 H), 1.43–1.50 (m, 2 H), 1.51–1.60 (m, 4 H), 1.68–1.85 (m, 6 H), 2.05 (br. s, 1 H), 2.26–2.41 (m, 1 H), 2.35–2.40 (m, 1 H), 2.58 (t, J = 7.9 Hz, 2 H), 2.94–2.99 (m, 2 H), 3.71 (s, 1 H), 3.86–3.94 (m, 2 H), 6.87, 7.12 (AA′BB′, J = 8.3 Hz, 4 H), 7.24 (dd, J = 1.7, 8.4 Hz, 1 H), 7.32–7.39 (m, 2 H), 7.54 (s, 1 H), 7.66–7.33 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.72, 25.25, 28.33 (d, J = 6.0 Hz), 31.50 (t, J = 23.3 Hz), 32.71, 34.12, 34.77, 37.84, 37.93 (d, J = 9.8 Hz), 39.81, 51.08, 67.51 (dd, J = 22.8, 34.4 Hz), 122.77 (dd, J = 242.2, 246.4 Hz), 125.37, 125.99, 127.18, 127.43, 127.46, 127.63, 127.71, 128.00, 129.75, 132.21, 133.56, 136.27, 139.65, 143.40 ppm (one signal in the aromatic region is not visible due to overlap). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –106.84 (d, J = 249.8 Hz, 1 F), –103.28 (d, J = 249.9 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3412, 2937, 2861, 1637, 1604, 1510, 1438, 1418, 1316, 1247, 1181, 1142, 1091, 1061, 1026, 946, 908, 881, 854, 817, 731, 648 cm^{-1}. MALDI-MS: m/z (%): calcd. for $C_{32}H_{38}F_2NO_2^+$ 506.2865; found 506.2870 (100, $[M + H]^+$); calcd. for $C_{32}H_{37}F_2NO_2Na^+$ 528.2685; found 528.2683 (30, $[M + Na]^+$); calcd. for $C_{32}H_{37}F_2NO_2K^+$ 544.2434; found 544.2428 (20, $[M + K]^+$).

(1*RS*)-*N*-[4-(2-Cyclopentylethyl)phenyl]-3,3-difluoro-*N*-[2-(2-naphthyl)ethyl]-4-oxocyclohexanecarboxamide [(±)-1]: To a solution of alcohol (±)-**18** (20 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) under Ar at 22 °C, Dess–Martin periodinane (15% solution in CH_2Cl_2, 123 μL, 168 mg, 0.08 mmol) was added and the resulting mixture stirred at 22 °C for 16 h. The mixture was treated with saturated aqueous $NaHCO_3$ solution (0.5 mL) and aqueous (10%) NaS_2O_3 solution (0.5 mL) and stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), filtered, and concentrated in vacuo. The resulting crude product was dissolved in CH_2Cl_2 (3 mL) and stirred in the presence of molecular sieves (4 Å) (50 mg) at 22 °C for 3 h. The mixture was filtered and the solvent removed in vacuo. Purification by CC (SiO_2; EtOAc/pentane, 1:8) yielded ketone (±)-**1** as a colorless wax (14 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.76–0.83 (m, 1 H), 1.03–1.13 (m, 2 H), 1.13–1.27 (m, 1 H), 1.40–1.51 (m, 1 H), 1.52–1.62 (m, 4 H), 1.69–1.78 (m, 3 H), 1.88–1.94 (m, 2 H), 2.16–2.30 (m, 1 H), 2.26–2.37 (m, 1 H), 2.40–2.46 (m, 1 H), 2.60 (t, J = 8.0 Hz, 2 H), 2.75–2.83 (m, 1 H), 2.97 (dt, J = 2.7, 7.7 Hz, 2 H), 3.89–3.96 (m, 2 H), 6.90, 7.17 (AA′BB′, J = 8.4 Hz, 4 H), 7.23 (dd, J = 1.7, 8.4 Hz, 1 H), 7.34–7.40 (m, 2 H), 7.54 (s, 1 H), 7.66–7.73 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.22, 25.45, 27.12 (d, J = 9.7 Hz), 28.73 (t, J = 12.3 Hz), 33.12, 34.30, 34.78, 37.80, 36.29 (d, J = 10.8 Hz), 39.79, 51.12, 122.75 (dd, J = 241.2, 249.4 Hz), 125.33, 125.99, 127.55, 127.12, 127.46, 127.63, 127.71, 128.46, 129.77, 132.11, 133.98, 136.28, 139.66, 143.41, 201.43 (dd, J = 12.8, 39.4 ppm (one signal in the aromatic region is not visible due to overlap). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.52 (d, J = 256.5 Hz, 1 F), –103.79 (d, J = 257.13 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3359, 2929, 2856, 1636, 1510, 1439, 1419, 1323, 1261, 1111, 1080, 1026, 976, 891, 856, 816, 744 cm^{-1}. MALDI-MS: m/z (%): calcd. for $C_{32}H_{36}F_2NO_2^+$ 504.2709; found 504.2718 (100,

$[M + H]^+$); calcd. for $C_{32}H_{35}F_2NO_2Na^+$ 526.2528; found 526.2524 (76, $[M + Na]^+$); calcd. for $C_{32}H_{35}F_2NO_2K^+$ 542.2267; found 542.2269 (69, $[M + K]^+$).

(1*S*,4*S*)-4-({[4-(2-Cyclopentylethyl)phenyl][2-(2-naphthyl)ethyl]-amino}carbonyl)-2,2-difluorocyclohexyl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate [(–)-20] and (1*R*,4*R*)-4-({[4-(2-Cyclopentylethyl)phenyl][2-(2-naphthyl)ethyl]amino}carbonyl)-2,2-difluorocyclohexyl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate [(–)-21]: To a solution of (–)-(*R*)-Mosher acid chloride (28 μL, 38 mg, 0.15 mmol) in THF (1 mL) under Ar at 0 °C, alcohol (±)-**18** (50 mg, 0.10 mmol) and DMAP (15 mg, 0.12 mmol) were added, and the mixture was stirred at 22 °C for 6 h. The solution was treated with saturated aqueous $NaHCO_3$ solution (2 mL) and the aqueous phase extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting diastereoisomers were separated by HPLC (Hibar, Si60; EtOAc/*n*-hexane, 1:4). The diastereoisomers (–)-**20** (31 mg, 43%) and (–)-**21** (31 mg, 43%) resulted as colorless wax, eluting in the given order.

(–)-20: $[\alpha]_D^{20}$ = –27.2 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.09 (m, 2 H), 1.20–1.31 (m, 1 H), 1.40–1.47 (m, 2 H), 1.50–1.59 (m, 4 H), 1.62–1.66 (m, 2 H), 1.67–1.74 (m, 3 H), 1.81–1.86 (m, 1 H), 2.03–2.08 (m, 1 H), 2.03–2.17 (m, 1 H), 2.37–2.45 (m, 1 H), 2.56 (t, *J* = 8.0 Hz, 2 H), 2.93–2.97 (m, 2 H), 3.47 (d, *J* = 1.0 Hz, 3 H), 3.84–3.96 (m, 2 H), 5.04–5.14 (m, 1 H), 6.84, 7.10 (AA′BB′, *J* = 8.3 Hz, 4 H), 7.23 (dd, *J* = 1.7, 8.4 Hz, 1 H), 7.26–7.30 (m, 3 H), 7.33–7.39 (m, 2 H), 7.41–7.43 (m, 2 H), 7.53 (s, 1 H), 7.65–7.68 (m, 2 H), 7.71–7.73 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.20, 26.42, 26.99 (d, *J* = 5.8 Hz), 32.68, 34.06, 34.72, 36.20 (t, *J* = 22.7 Hz), 37.47 (d, *J* = 9.2 Hz), 37.74, 39.80, 50.98, 55.54, 72.67 (t, *J* = 20.3 Hz), 84.75 (d, *J* = 28.0 Hz), 119.83 (dd, *J* = 245.7, 247.2 Hz), 123.14 (d, *J* = 288.8 Hz), 125.43, 126.04, 127.15, 127.20, 127.32, 127.41, 127.55, 127.62, 128.03, 128.34, 129.58, 129.85, 132.04, 132.23, 133.54, 136.05, 139.33, 143.70, 165.65, 172.45 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –115.92 (d, *J* = 239.9 Hz, 1 F), –102.83 (d, *J* = 239.3 Hz, 1 F), –71.90 (s, 3 F) ppm. IR (neat): ṽ = 2946, 2863, 1753, 1652, 1603, 1510, 1451, 1409, 1363, 1330, 1241, 1168, 1096, 1045, 1000, 955, 856, 818, 744, 716, 696 cm^{-1}. MALDI-MS: *m*/*z* (%): calcd. for $C_{42}H_{45}F_5NO_4^+$ 722.3263; found 722.3271 (100, $[M + H]^+$); calcd. for $C_{42}H_{45}F_5NO_4Na^+$ 744.3083; found 744.3082 (86, $[M + Na]^+$); calcd. for $C_{42}H_{45}F_5NO_4K^+$ 760.2822; found 760.2833 (57, $[M + K]^+$).

(–)-21: $[\alpha]_D^{20}$ = –2.8 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04–1.10 (m, 2 H), 1.38–1.48 (m, 3 H), 1.52–1.60 (m, 4 H), 1.64–1.75 (m, 5 H), 1.93–1.98 (m, 1 H), 2.02–2.09 (m, 1 H), 2.03–2.16 (m, 1 H), 2.39–2.47 (m, 1 H), 2.57 (t, *J* = 7.9 Hz, 2 H), 2.92–2.99 (m, 2 H), 3.39 (d, *J* = 0.7 Hz, 3 H), 3.90 (dt, *J* = 4.0, 7.9 Hz, 2 H), 5.05–5.15 (m, 1 H), 6.85, 7.11 (AA′BB′, *J* = 8.3 Hz, 4 H), 7.23 (dd, *J* = 1.7, 8.4 Hz, 1 H), 7.27–7.33 (m, 3 H), 7.33–7.39 (m, 2 H), 7.41–7.43 (m, 2 H), 7.53 (s, 1 H), 7.65–7.68 (m, 2 H), 7.71–7.73 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.23, 26.48, 27.28 (d, *J* = 1.7 Hz), 32.69, 34.06, 34.73, 36.20 (t, *J* = 22.8 Hz), 37.48 (d, *J* = 9.0 Hz), 37.76, 39.80, 50.99, 55.29, 72.79 (t, *J* = 20.4 Hz), 84.88 (d, *J* = 28.3 Hz), 119.67 (dd, *J* = 245.5, 247.6 Hz), 123.10 (d, *J* = 288.2 Hz), 125.43, 126.04, 127.15, 127.33, 127.41, 127.56, 127.62, 128.04, 128.33, 129.64, 129.86, 131.64, 132.24, 133.55, 136.06, 139.35, 143.70, 165.60, 172.46 ppm (one signal in the aromatic region is not visible due to overlap). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –116.35 (d, *J* = 240.6 Hz, 1 F), –103.66 (d, *J* = 240.7 Hz, 1 F), –72.41 (s, 3 F) ppm. IR (neat): ṽ = 2946, 2863, 1755, 1652, 1510, 1451, 1409, 1270, 1242, 1168, 1098, 1045, 955, 910, 856, 818, 730, 717, 648 cm^{-1}. MALDI-MS: *m*/*z* (%): calcd. for $C_{42}H_{45}F_5NO_4^+$ 722.3263; found 722.3269 (55, $[M + H]^+$); calcd. for $C_{42}H_{45}F_5NO_4Na^+$ 744.3083; found 744.3075 (100, $[M + Na]^+$); calcd. for $C_{42}H_{44}F_5NO_4K^+$ 760.2822; found 760.2820 (72, $[M + K]^+$).

(1*S*,4*R*)-4-({[4-(2-Cyclopentylethyl)phenyl][2-(2-naphthyl)ethyl]-amino}carbonyl)-2,2-difluorocyclohexyl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate [(+)-22] and (1*R*,4*S*)-4-({[4-(2-Cyclopentylethyl)phenyl][2-(2-naphthyl)ethyl]amino}carbonyl)-2,2-difluorocyclohexyl (2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoate [(–)-23]: To a solution of (–)-(*R*)-Mosher acid chloride (39 μL, 53 mg, 0.21 mmol) in THF (1 mL) under Ar at 0 °C, alcohol (±)-**19** (70 mg, 0.14 mmol) and DMAP (25 mg, 0.21 mmol) were added, and the mixture was stirred at 22 °C for 6 h. The solution was treated with saturated aqueous $NaHCO_3$ solution (2 mL) and the aqueous phase extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting diastereoisomers were separated by HPLC (Hibar, Si60; EtOAc/*n*-hexane, 1:4). The diastereoisomers (+)-**22** (46 mg, 46%) and (–)-**23** (46 mg, 46%) resulted as colorless wax, eluting in the given order.

(+)-22: $[\alpha]_D^{20}$ = +25.8 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.17 (m, 2 H), 1.40–1.45 (m, 1 H), 1.49–1.58 (m, 4 H), 1.55–1.68 (m, 4 H), 1.75–1.87 (m, 4 H), 1.93–1.99 (m, 1 H), 2.17–2.34 (m, 1 H), 2.44–2.50 (m, 1 H), 2.66 (t, *J* = 7.9 Hz, 2 H), 2.95–3.07 (m, 2 H), 3.56 (s, 3 H), 3.87–4.02 (m, 2 H), 5.21 (s, 1 H), 6.96, 7.19 (AA′BB′, *J* = 8.3 Hz, 4 H), 7.29 (dd, *J* = 1.7, 8.4 Hz, 1 H), 7.40–7.46 (m, 5 H), 7.52–7.55 (m, 2 H), 7.59 (s, 1 H), 7.71–7.74 (m, 2 H), 7.78–7.80 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.02, 25.23, 26.85 (d, *J* = 5.4 Hz), 32.66 (t, *J* = 22.9 Hz), 32.70, 34.06, 34.75, 37.79, 39.79, 51.08, 55.44, 70.06 (dd, *J* = 22.3, 40.6 Hz), 84.86 (d, *J* = 18.1 Hz), 120.26 (dd, *J* = 238.3, 252.2 Hz), 123.27 (d, *J* = 288.5 Hz), 125.38, 125.99, 127.15, 127.30, 127.36, 127.42, 127.61, 127.65, 127.99, 128.52, 129.76, 129.80, 131.83, 132.22, 133.55, 136.13, 139.49, 143.54, 165.33, 172.55 ppm (one signal in the aromatic region is not visible due to overlap). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.88 (d, *J* = 255.7 Hz, 1 F), –101.34 (d, *J* = 255.7 Hz, 1 F), –71.44 (s, 3 F) ppm. IR (neat): ṽ = 2845, 2862, 1758, 1655, 1510, 1439, 1408, 1363, 1318, 1238, 1170, 1123, 1102, 1018, 948, 909, 855, 818, 730, 717, 697 cm^{-1}. MALDI-MS: *m*/*z* (%): calcd. for $C_{42}H_{45}F_5NO_4^+$ 722.3263; found 722.3261 (74, $[M + H]^+$); calcd. for $C_{42}H_{44}F_5NO_4Na^+$ 744.3083; found 744.3071 (90, $[M + Na]^+$); calcd. for $C_{42}H_{44}F_5NO_4K^+$ 760.2822; found 760.2810 (100, $[M + K]^+$).

(–)-23: $[\alpha]_D^{20}$ = –46.6 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.10 (m, 2 H), 1.42–1–50 (m, 3 H), 1.53–1.60 (m, 4 H), 1.63–1.76 (m, 5 H), 1.80–1–87 (m, 2 H), 2.03–2.19 (m, 1 H), 2.38–2.44 (m, 1 H), 2.58 (t, *J* = 7.9 Hz, 2 H), 2.90–2.98 (m, 2 H), 3.48 (d, *J* = 0.9 Hz, 3 H), 3.81–3.94 (m, 2 H), 5.17 (s, 1 H), 6.85, 7.12 (AA′BB′, *J* = 8.3 Hz, 4 H), 7.21 (dd, *J* = 1.8, 8.4 Hz, 1 H), 7.31–7.37 (m, 5 H), 7.44–7.47 (m, 2 H), 7.52 (s, 1 H), 7.63–7.67 (m, 2 H), 7.69–7.72 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.29, 25.23, 26.95 (d, *J* = 5.3 Hz), 32.56 (t, *J* = 23.0 Hz), 32.70, 34.08, 34.75, 37.45 (d, *J* = 9.4 Hz), 37.80, 39.79, 51.07, 55.46, 69.92 (dd, *J* = 22.8, 40.4 Hz), 84.88 (d, *J* = 28.2 Hz), 120.08 (dd, *J* = 238.5, 253.0 Hz), 123.23 (d, *J* = 288.4 Hz), 125.39, 126.00, 127.15, 127.35, 127.41, 127.49, 127.61, 127.64, 128.00, 128.45, 129.74, 129.82, 131.65, 132.22, 133.56, 136.12, 139.48, 143.57, 165.22, 172.62 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.78 (d, *J* = 255.2 Hz, 1 F), –102.26 (d, *J* = 255.2 Hz, 1 F), –71.79 (s, 3 F) ppm. IR (neat): ṽ = 2944, 2862, 1759, 1655, 1510, 1451, 1439, 1408, 1383, 1363, 1318, 1239, 1170, 1103, 1018, 947, 909, 855, 818, 731, 717,

697 cm^{-1}. MALDI-MS: *m/z* (%): calcd. for $C_{42}H_{45}F_5NO_4^+$ 722.3263; found 722.3277 (100, $[M + H]^+$); calcd. for $C_{42}H_{44}F_5NO_4Na^+$ 744.3083; found 744.3087 (53, $[M + Na]^+$); calcd. for $C_{42}H_{44}F_5NO_4K^+$ 760.2822; found 760.2835 (64, $[M + K]^+$).

(1*SR*,4*SR*,5*RS*)-5-(2-Furylmethyl)-2-oxo-4-[(*E*)-2-(4-pentylphenyl)-vinyl]cyclohexyl Acetate [(±)-39]: To a solution of olefin (±)-**33** (500 mg, 1.91 mmol) in CH_2Cl_2 (10 mL) under Ar at 22 °C, vinylbenzene **38** (730 mg, 4.19 mmol) and Grubbs 2 catalyst (81 mg, 0.10 mmol) were added, and the mixture was stirred under reflux for 6 h. After cooling to 22 °C, the mixture was filtered through Celite and the organic phase concentrated in vacuo. Purification by CC (SiO_2; CH_2Cl_2/Et_2O, 95:5) yielded (±)-**39** as a colorless oil (190 mg, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.9 Hz, 3 H), 1.29–1.39 (m, 4 H), 1.58–1.65 (m, 2 H), 1.88–1.94 (m, 1 H), 2.16–2.24 (m, 1 H), 2.17 (s, 3 H), 2.39–2.44 (m, 1 H), 2.60 (t, *J* = 7.7 Hz, 2 H), 2.68 (d, *J* = 5.8 Hz, 2 H), 2.73–2.77 (m, 1 H), 2.84–3.05 (m, 2 H), 5.20–5.24 (m, 1 H), 6.03–6.11 (m, 1 H), 6.12 (d, *J* = 3.2 Hz, 1 H), 6.33 (dd, *J* = 1.9, 3.1 Hz, 1 H), 6.43 (d, *J* = 15.8 Hz, 1 H), 7.14, 7.28 (AA′BB′, *J* = 8.1 Hz, 4 H), 7.37 (dd, *J* = 0.8, 1.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.00, 20.78, 22.52, 31.10, 31.32, 31.45, 33.45, 35.62, 37.30, 41.77, 44.80, 74.15, 106.90, 110.28, 126.17, 128.63, 130.07, 131.48, 134.15, 141.58, 142.62, 153.24, 169.91, 204.43 ppm. IR (neat): $\tilde{\nu}$ = 2928, 2856, 2360, 1747 (CO), 1728 (CO), 1596, 1508, 1369, 1230, 1146, 1074, 1010, 968, 734 cm^{-1}. EI-MS: *m/z* (%): calcd. for $C_{26}H_{32}O_4^+$ 408.2295; found 408.2299 (31, $[M^+]$); calcd. for $C_5H_5O^+$ 81.0335; found 81.0328 (100).

(1*SR*,4*SR*,5*RS*)-2,2-Difluoro-5-(2-furylmethyl)-4-[(*E*)-2-(4-pentylphenyl)vinyl]cyclohexyl Acetate ((±)-40) and (1*SR*,4*SR*,5*RS*)-2-Fluoro-5-(2-furylmethyl)-4-[(*E*)-2-(4-pentylphenyl)vinyl]cyclohex-2-enyl Acetate [(±)-41]: To a solution of ketone (±)-**39** (160 mg, 0.39 mmol) in CH_2Cl_2 (1 mL) under Ar at 22 °C, DAST (0.10 mL, 126 mg, 0.79 mmol) was added and the mixture stirred under reflux for 5 h. After cooling to 22 °C, additional DAST (0.10 mL, 126 mg, 0.79 mmol) was added, and the mixture was stirred under reflux for 15 h. After cooling to 22 °C, the solution was poured into an ice-cold saturated aqueous $NaHCO_3$ solution and stirred for 1 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by CC (SiO_2; CH_2Cl_2) yielded (±)-**40** (62 mg, 36%) and (±)-**41** (60 mg, 36%) as yellow oils, eluting in the given order.

(±)-40: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.0 Hz, 3 H), 1.19–1.28 (m, 4 H), 1.46–1.57 (m, 3 H), 1.81–1.93 (m, 2 H), 1.96–2.06 (m, 2 H), 2.03 (s, 3 H), 2.17–2.26 (m, 1 H), 2.32–2.38 (m, 1 H), 2.51 (t, *J* = 7.7 Hz, 2 H), 2.78–2.83 (m, 1 H), 5.09 (s, 1 H), 5.88 (d, *J* = 2.7 Hz, 1 H), 5.90–5.94 (m, 1 H), 6.17–6.19 (m, 1 H), 6.40 (d, *J* = 15.8 Hz, 1 H), 7.06, 7.21 (AA′BB′, *J* = 8.4 Hz, 4 H), 7.21 (dd, *J* = 0.8, 1.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.05, 21.01, 22.57, 31.15, 31.50, 32.75, 32.81, 34.58, 35.67, 36.28 (q, *J* = 21.1, 27.4 Hz), 42.94 (d, *J* = 9.3 Hz), 68.88 (dd, *J* = 23.2, 38.4 Hz), 106.77, 110.17, 120.32 (dd, *J* = 38.9, 252.4 Hz), 126.16, 128.69, 130.10, 132.01, 134.33, 141.28, 142.57, 153.47, 169.26 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –104.75 (d, *J* = 252.0 Hz, 1 F), –106.20 (d, *J* = 252.4 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 2929, 2857, 1753 (CO), 1596, 1509, 1436, 1370, 1227, 1146, 1054, 1011, 970, 727 cm^{-1}. EI-MS: *m/z* (%): calcd. for $C_{26}H_{32}F_2O_3^+$ 430.2314; found 430.2316 (39, $[M^+]$); calcd. for $C_5H_5O^+$ 81.0335; found 81.0327 (100).

(±)-41: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.0 Hz, 3 H), 1.20–1.30 (m, 4 H), 1.50–1.57 (m, 2 H), 1.57–1.63 (m, 1 H), 1.87–1.92 (m, 1 H), 1.93–1.96 (m, 1 H), 2.01 (s, 3 H), 2.51 (t, *J* = 7.7 Hz, 2 H), 2.53 (dd, *J* = 7.9, 15.2 Hz, 1 H), 2.68–2.75 (m, 1 H), 2.80 (dd, *J* = 4.0, 15.2 Hz, 1 H), 5.33 (dd, *J* = 2.6, 15.2 Hz, 1 H), 5.36–5.39 (m, 1 H), 5.93 (d, *J* = 3.1 Hz, 1 H), 5.95 (dd, *J* = 7.7, 14.5 Hz, 1 H), 6.20 (dd, *J* = 1.9, 3.2 Hz, 1 H), 6.42 (d, *J* = 15.8 Hz, 1 H), 7.06, 7.22 (AA′BB′, *J* = 8.1 Hz, 4 H), 7.22 (dd, *J* = 1.2, 2.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.03, 21.14, 33.55, 30.75, 31.14, 31.48, 33.57 (d, *J* = 7.2 Hz), 34.39, 35.65, 43.20 (d, *J* = 6.6 Hz), 65.86 (d, *J* = 26.3 Hz), 106.79, 110.18, 111.83 (d, *J* = 13.5 Hz), 126.18, 128.67, 129.85, 132.32, 134.33, 141.29, 142.57, 153.52, 156.05 (d, *J* = 260.5 Hz), 170.30 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.34 (s, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3023, 2928, 2856, 2360, 1742 (CO), 1698, 1508, 1437, 1370, 1227, 1147, 1040, 1011, 970, 807, 728 cm^{-1}. EI-MS: *m/z* (%): calcd. for $C_{26}H_{31}FO_3^+$ 410.2252; found 410.2254 (4, $[M^+]$); calcd. for $C_5H_5O^+$ 81.0335; found 81.0324 (100).

(1*SR*,4*SR*,5*RS*)-2,2-Difluoro-5-(2-furylmethyl)-4-[(*E*)-2-(4-pentylphenyl)vinyl]cyclohexanol [(±)-25]: To a solution of acetate (±)-**41** (60 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) under Ar at 22 °C, a solution of K_2CO_3 in aqueous MeOH (1.00 g, K_2CO_3 in 30 mL H_2O and 115 mL MeOH) (3 mL) was added and the mixture stirred at 22 °C for 6 h. Saturated aqueous NH_4Cl solution (5 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by CC (SiO_2; CH_2Cl_2) yielded (±)-**25** as a yellow oil (29 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.0 Hz, 3 H), 1.29–1.40 (m, 4 H), 1.51–1.67 (m, 4 H), 1.99–2.11 (m, 4 H), 2.15–2.32 (m, 1 H), 2.40–2.46 (m, 1 H), 2.61 (t, *J* = 7.6 Hz, 2 H), 2.92 (d, *J* = 15.0 Hz, 1 H), 3.97 (s, 1 H), 5.98–6.04 (m, 2 H), 6.28 (s, 1 H), 6.49 (d, *J* = 15.8 Hz, 1 H), 7.16, 7.31 (AA′BB′, *J* = 8.1 Hz, 4 H), 7.32 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.03, 22.55, 31.15, 31.48, 31.56, 33.72, 34.20 (d, *J* = 6.1 Hz), 35.20 (dd, *J* = 20.9, 23.7 Hz), 35.65, 43.28, 68.33 (dd, *J* = 23.1, 34.2 Hz), 106.56, 110.01, 122.46 (dd, *J* = 242.3, 246.5 Hz), 126.12, 128.65, 130.55, 131.70, 134.42, 141.15, 142.45, 153.91 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.17 (d, *J* = 248.8 Hz, 1 F), –107.34 (d, *J* = 248.7, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3432, 2928, 2856, 2360, 2342, 1596, 1508, 1435, 1278, 1146, 1072, 1054, 1008, 969, 727 cm^{-1}. EI-MS: *m/z* (%): calcd. für $C_{24}H_{30}F_2O_2^+$ 388.2208; found 388.2210 (100, $[M^+]$).

(4*SR*,5*SR*)-2,2-Difluoro-5-(2-furylmethyl)-4-[(*E*)-2-(4-pentylphenyl)-vinyl]cyclohexanone [(±)-24]: To a solution of alcohol (±)-**25** (28 mg, 0.07 mmol) in CH_2Cl_2 (0.25 mL) under Ar at 22 °C, Dess–Martin periodinane (15% solution in CH_2Cl_2, 221 μL, 301 mg, 0.14 mmol) was added and the resulting mixture stirred at 22 °C for 16 h. The mixture was treated with saturated aqueous $NaHCO_3$ solution (0.2 mL) and with aqueous (10%) NaS_2O_3 solution (0.2 mL), then stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic phases were dried with $MgSO_4$, filtered, and concentrated in vacuo. The resulting crude product was dissolved in CH_2Cl_2 (1 mL) and stirred in the presence of molecular sieves (4 Å) (20 mg) at 22 °C for 3 h. The mixture was filtered and the solvent removed in vacuo. Purification by CC (SiO_2; EtOAc/pentane, 1:8) yielded ketone (±)-**24** as a colorless wax (24 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 1.28–1.38 (m, 4 H), 1.56–1.66 (m, 2 H), 1.90–2.15 (m, 1 H), 1.97 (ddd, *J* = 2.0, 4.3, 35.2 Hz, 1 H), 2.48–2.75 (m, 7 H), 2.94 (dd, *J* = 3.7, 15.0 Hz, 1 H), 5.94 (dd, *J* = 8.9, 15.8 Hz, 1 H), 6.03 (d, *J* = 2.8 Hz, 1 H), 6.29 (dd, *J* = 2.0, 3.2 Hz, 1 H), 6.58 (d, *J* = 15.8 Hz, 1 H), 7.16, 7.31 (AA′BB′, *J* = 8.2 Hz, 4 H), 7.33 (dd, *J* = 0.9, 1.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.00, 21.53, 30.10, 30.46, 31.24, 34.64, 40.44 (dd, *J* = 19.6, 24.7 Hz), 41.30, 41.50 (d, *J* = 9.1 Hz), 42.24, 106.44, 109.26, 114.18

(dd, J = 243.9, 259.5 Hz), 125.21, 126.96, 127.74, 131.17, 132.83, 140.72, 141.96, 151.11, 196.66 (dd, J = 23.0, 28.0 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –104.66 (d, J = 253.7 Hz, 1 F), –116.14 (d, J = 254.0 Hz, 1 F) ppm. IR (neat): $\tilde{\nu}$ = 3397, 2928, 2857, 2360, 2342, 1718, 1512, 1437, 1261, 1080, 1015, 970, 799, 728 cm^{-1}. EI-MS: *m/z* (%): calcd. for $C_{24}H_{28}F_2O_2^+$ 386.2052; found 386.2049 (29, [M^+]); calcd. for $C_5H_5O^+$ 81.0335; found 81.0330 (100).

Supporting Information (see footnote on the first page of this article): Additional synthetic protocols, separation and determination of absolute configuration of Moshers esters, and determination of relative configuration of (±)-**31**, (±)-**32**, (±)-**33** to (±)-**36**.

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