Synthesis of Fluorinated Cycloalkyl *N*-Phenylcarbamates and Their Microbial Defluorination/Oxygenation by *Beauveria bassiana*

Günter Haufe,*[a] Sylke Pietz,[a] Dörthe Wölker,[a] and Roland Fröhlich[a][‡]

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Earlier investigations showed that cycloalkyl *N*-phenylcarbamates were hydroxylated by the fungus *Beauveria bassiana* predominantly in the 4-position relative to the electron-rich substituent. In cases involving fluorinated methylene groups potentially capable of hydroxylation, however, defluorination and formation of a ketone was observed. The formation of the ketone can be explained by primary hydroxylation to form an unstable geminal fluorohydrin, which is subsequently dehydrofluorinated.

Introduction

Several different microorganisms have been shown to be able to biohydroxylate nonactivated hydrocarbon positions.[1] Among them, one of the most frequently used is the fungus *Beauveria bassiana*.[2] The biocatalytic abilities of this fungus have recently been reviewed, showing its very broad substrate acceptance and selectivity of biotransformations.[3] Some recent examples of such transformations are mentioned in reference.[4]

Distance models for hydroxylations of chemically nonactivated hydrocarbon positions in substituted alicyclics such as amides or carbamates have been developed,[5] extended,[6] and modified.[7] Hydroxylations of flexible and rigid mono- or polycyclic *N*-phenylcarbamates by *B. bassiana* occurred at a preferred distance of about 5 Å between the hydrogen atom that was replaced and the oxygen atom of the carbamate function directly attached to the carbocyclic skeleton.[7] The presence of a fluorine substituent in the *trans*-2-position in relation to the docking group did not change the regioselectivity, but influenced the diastereoselectivity, depending on the ring size and the absolute configurations of the stereogenic centers.[8]

It is generally known that the presence of fluorine atoms in a molecule can change the regioselectivities of microbial hydroxylations. For example, monofluorination of the 6α-position in 5α-androstan-17-one prevented 7β-hydroxylation by *Aspergillus ochraceus*. Instead, the 11α-position was hydroxylated exclusively. In contrast, this position was hydroxylated only to a minor extend in the parent steroid.[9] Other examples of this type of "blocking fluorination" have also been described,[10] and fluorinated terpenes have also been shown to be hydroxylated in different positions from the nonfluorinated parent compounds.[11] In a case in which the natural hydroxylation position (5) of camphor was blocked by geminal difluorination, *Pseudomonas putida* hydroxylated this derivative at the methyl group *anti* to the existing keto group.[12]

In the preceding paper we showed that the presence of a fluorine substituent, attached at the 5-*endo*- or 5-*exo*-position of *exo*-tricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-phenylcarbamates, prevented hydroxylation in any alicyclic position. Instead, only products *p*-hydroxylated in the aromatic ring were observed, although in low yields. The nonfluorinated parent carbamate was hydroxylated selectively in the 5-*exo*-position.[4]

We would now like to present our results on biotransformations, with *B. bassiana*, of fluorinated cycloalkyl *N*-phenylcarbamates bearing a fluorine atom in the 4-position relative to an electron-rich docking group, or in other words at a carbon atom that was shown to be hydroxylated in the case of the nonfluorinated parent carbamates e.g. at a carbon atom that was shown to be hydroxylated in the case of the nonfluorinated parent carbamates.[6,7]

Results and Discussion

Synthesis of the Fluorinated Cycloalkyl *N*-Phenylcarbamates

The desired 4-fluorocycloalkyl *N*-phenylcarbamates should be available from the corresponding 4-fluorocycloalkanols. We therefore designed syntheses of *cis*-4-fluorocyclohexanol (**3**) from *p*-fluorophenol (**1**) and of *cis*-4-fluorocyclooctanol (**13**) from cyclooctene oxide (**11**).

[a] Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster,
Corrensstr. 40, 48149 Münster, Germany
Fax: (internat.) +49-251-8339772
E-mail: haufe@uni-muenster.de
[‡] X-ray analysis.
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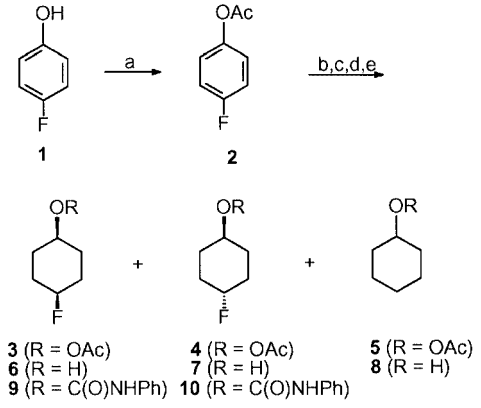
It is known from the literature that hydrogenation of fluorinated aromatics is difficult to achieve without partial loss of the fluorine substituent. Under very mild conditions, with rhodium(III) chloride and Aliquat 336 (methyltrioctylammonium chloride) in a two-phase system of water and dichloromethane, fluorobenzene was hydrogenated, giving a 40:60 mixture of fluorocyclohexane and cyclohexane.[13] Application of this procedure to *p*-fluorophenol (**1**), however, resulted in a mixture of cyclohexanone and cyclohexanol, only traces of fluorinated products being detected. In contrast, hydrogenation of 1-acetoxy-4-fluorobenzene (**2**), commercially available nowadays but then produced from **1** and acetic anhydride in the presence of pyridine, after 40% conversion, gave a 10:1:7 mixture of *cis*-1-acetoxy-4-fluorocyclohexane (**3**), its *trans* isomer **4**, and acetoxycyclohexane (**5**) (Scheme 1).



Scheme 1. Reagents and conditions: (a) Ac_2O/Py, 3 h, reflux; (b) $RhCl_3$/Aliquat 336/1,2-dichloroethane/water; (c) KOH/MeOH, 2 h, room temp.; (d) chromatography; (e) PhCNO, petroleum ether 110−140 °C, reflux, 4 h

After saponification with KOH/MeOH, a mixture of *cis*-4-fluorocyclohexanol (**6**), the corresponding *trans*-compound **7**, and cyclohexanol (**8**) in the ratio given above was obtained. Column chromatographic separation gave a 10:1 mixture of **6** and **7** in 45% overall yield relative to consumed **1**. Heating of this mixture at reflux with phenyl isocyanate in petroleum ether (110−140 °C) gave 77% of a mixture of the carbamates **9** and **10**. The pure main product **9** was isolated after recrystallization from petroleum ether. The structure of **9** was deduced from spectroscopic data (cf. Exp. Sect.) and the *cis* configuration was established by X-ray analysis (Figure 1).

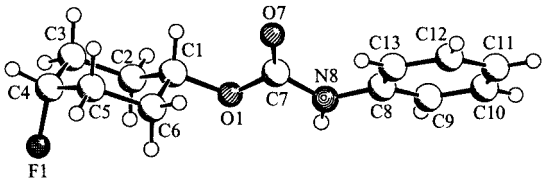
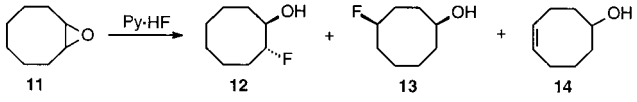


Figure 1. Crystal structure of compound **9**

Ring opening of epoxides with hydrofluorinating reagents is known to proceed *anti*-selectively.[14] Depending on the acidity of the reagent and the nucleophilicity of the fluorinating species, either an S_N1 or an S_N2 mechanism is more likely.[15] For S_N2-type reactions, triethylamine−trihydrofluoride ($Et_3N{\cdot}3HF$) has been shown to be a very efficient reagent.[16] By way of example, *cis*-cycloalkene oxides gave the corresponding *trans*-configured 1,2-fluorohydrins.[17] On the other hand, S_N1-type ring opening was suggested to occur when the more acidic pyridine·9HF complex (Olah's reagent) was used.[18] With application of this reagent, the yields of 1,2-fluorohydrins are sometimes low because of rearrangements of the intermediary carbocationic species or succeeding reactions of the formed primary products.[19]

Furthermore, it is also known that electrophilic reactions with medium-sized rings such as cyclooctene or cyclooctene oxide can occur with intermediary transannular hydride shifts,[20] so electrophilic halogenation of *cis*-cyclooctene[21] and acid-catalyzed ring-opening of cyclooctene oxide (**11**),[22] besides the expected *trans*-1,2-products, also gave 1,4-products, which in some cases even become the major products.

We recently showed that cyclooctene oxide (**11**) gave *trans*-2-fluorocyclooctanol (**12**) on treatment with $Et_3N{\cdot}3HF$.[17] Treatment of **11** with mixtures of pyridine and HF in different concentrations gave **12**, together with *cis*-4-fluorocyclooctanol (**13**), cyclooct-4-enol (**14**), and several other minor products that were not identified (Scheme 2).



Scheme 2

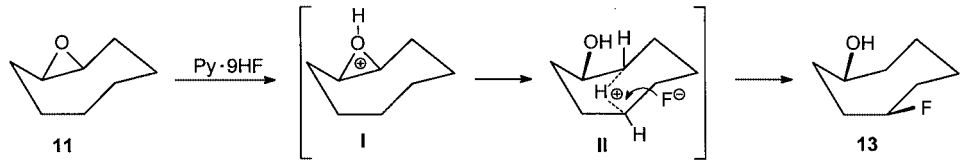
The product ratio is determined by the nature of the fluorinating reagent used and the molar excess of the reagent used (Table 1).

While $Et_3N{\cdot}3HF$ gave the *trans*-1,2-fluorohydrin **12** exclusively (Entry 1), the more acidic reagents (Entries 2−5) produced mixtures of **12**, **13**, and **14**. The most selective formation of the desired *cis*-1,4-fluorohydrin **13** was observed with commercial Olah's reagent (70% Py·9HF, Entry 6). This product is formed after an intermediary transannular hydride shift. Since only the *cis* isomer was formed (no traces of a third, probably *trans*-configured, 4-fluorocyclooctanol were found in the ^{19}F NMR spectrum of the crude product mixture) an intermediary nonclassical, μ-hydrido-bridged[23] carbonium ion is most probable. The protonated epoxide **I** is attacked by an intra-annular hydride in a transannular position, giving rise to the bridged species **II**. Consequently, back side attack of the fluorinating species at C-2 is blocked. Nucleophilic attack thus occurs from the back side at C-4, selectively giving the *cis*-4-fluorocyclooctanol (**13**) (Scheme 3).

Table 1. Results of ring opening of cyclooctene oxide (**11**) with different hydrofluorinating reagents

Entry	Reagent	Molar ratio	Temp. [°C]	Reaction time [h]	Solvent	Products		
						12	**13**	**14**
1	$Et_3N{\cdot}3HF$	15:1	60	40	–	100[a]	0	0
2	$Et_3N{\cdot}3HF$, + 5% H_2SO_4	15:1	60	30	–	30	30	30
3	40% Py·HF	2:1	60	80	CH_2Cl_2	40	20	15
4	40% Py·HF	5:1	60	80	–	70	15	10
5	40% Py·HF, + 5% H_2SO_4	2:1	60	60	CH_2Cl_2	50	20	25
6	70% Py·HF	2:1	20	24	CH_2Cl_2	5	60	30

[a] 30% conversion.



Scheme 3

This type of hydride shift has also been observed in ring opening of an eight-membered bicyclic aziridine with Olah's reagent,[19a] and had been discovered in acid-catalyzed ring opening reactions of cyclooctene oxide, by Cope et al., as early as at the beginning of the 1950s.[20,22] Deprotonation of the intermediary cationic species affords compound **14**.

The structure of **13** was deduced from the following characteristic spectroscopic data.

The elemental composition is obvious from the molecular ion (m/z = 146) in the electron impact mass spectrum and the elemental analysis. In the IR spectrum (high dilution in dry CCl_4), the absorption of a nonassociated OH group at ν = 3621 cm^{-1} shows that the functional groups are not adjacent. Consequently, the signal of the carbon atom bearing the OH group is observed in the ^{13}C NMR spectrum as a singlet at δ = 71.9 ppm, while the signal of the CHF group is found as a doublet at δ = 94.1 ppm ($^1J_{C,F}$ = 146 Hz). The corresponding multiplets of the methine protons appear at δ = 4.60 ppm ($^2J_{H,F}$ = 45.6 Hz) and δ = 3.75 ppm. The 1,4-*cis* relationship of the substituents could not be determined from the spectra, but was verified by X-ray analysis (Figure 2) of the carbamate **15**, which was formed by heating of compound **13** at reflux in petroleum ether with phenyl isocyanate (Scheme 4).

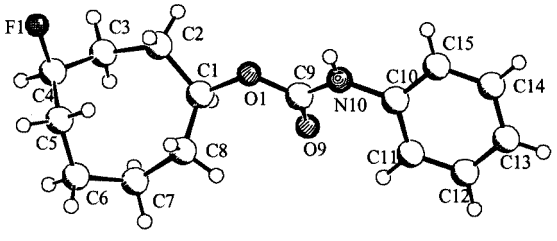
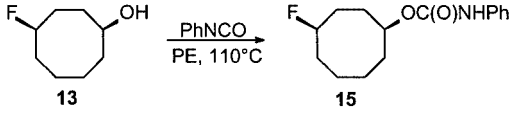


Figure 2. Crystal structure of compound **15**

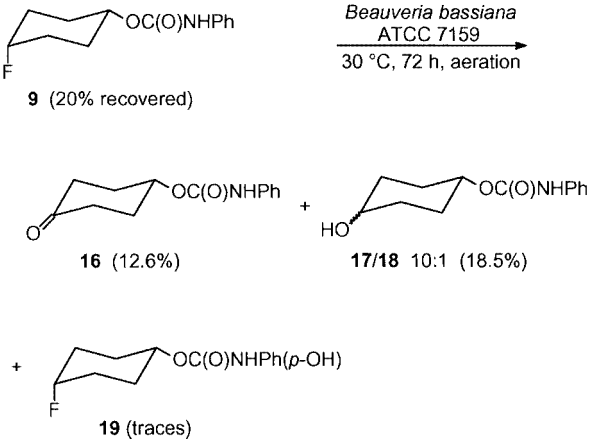


Scheme 4

Biotransformation with *Beauveria bassiana*

All biotransformations of compounds **9** and **15** were performed by a standard procedure[8b] in a 2-L fermenter with 200 mg of the substrates per liter of a growing culture of *B. bassiana* ATCC 7159. In a standard medium,[7] the culture with the substrate was aerated with 1.5 L air per minute at 30 °C for 72 h.

The biotransformation of compound **9** by this procedure gave, besides 20% of starting material, a mixture of four products in about 32% combined yield (Scheme 5).



Scheme 5

The resulting ketone **16** was isolated in 12.6% yield and was identified unequivocally by X-ray analysis (Figure 3). The main product (18.5%) was a 10:1 mixture of the alcohols **17** and **18**, probably formed from **16** by an alcohol dehydrogenase. The *cis*-4-hydroxycyclohexyl *N*-phenylcarbamate (**17**) was separated in pure form by recrystallization. The structure of **17** was deduced from the spectroscopic data and confirmed by X-ray analysis (Figure 4). The *trans* isomer **18** could not be isolated as a pure compound; its structure was deduced from spectroscopic data taken from the spectra of an enriched mixture of **17** and **18** and comparison with the known data for **18**.[24] The fourth product, **19**, formed in traces, was not isolated. Its structure is likely according to the mass spectrum obtained by GC/MS coupling; together with others (see Exp. Sect.), the molecular ion (m/z = 253) and a characteristic fragment of 4-hydroxyphenyl isocyanate (m/z = 135) were found.

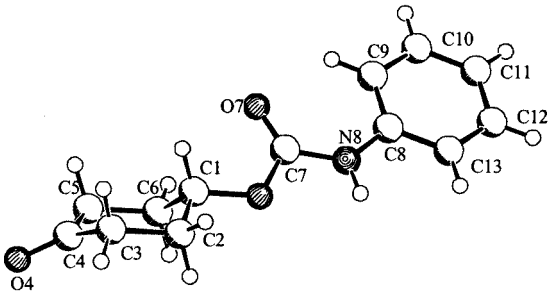


Figure 3. X-ray crystal structure of compound **16**

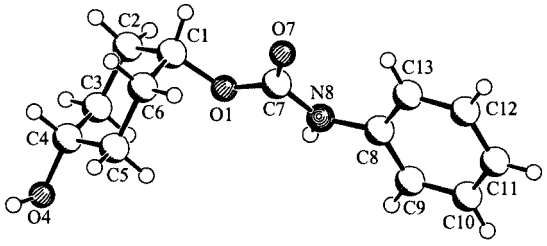
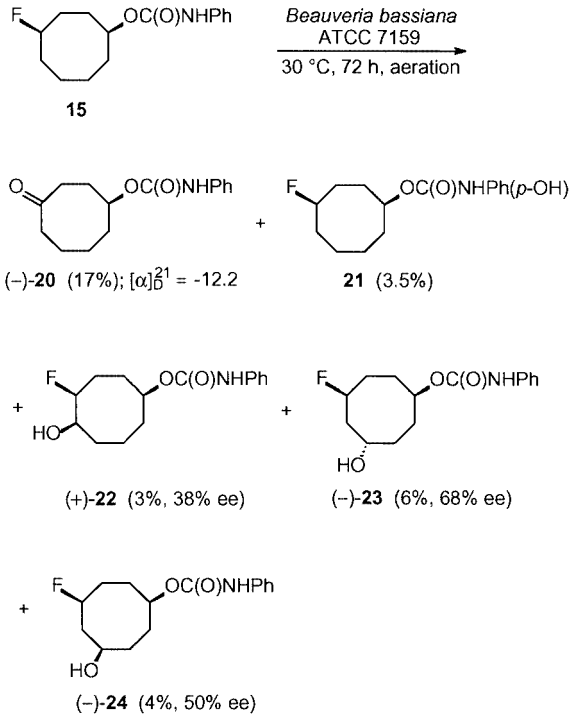


Figure 4. X-ray crystal structure of compound **17**

In conclusion, in contrast to the results obtained in the cases of 5-*endo*- and 5-*exo*-fluoronortricyclan-3-yl *N*-phenylcarbamate,[4] investigation of the biotransformation of *cis*-4-fluorocyclohexyl *N*-phenylcarbamate showed that monofluorination of a potential hydroxylation position did not prevent attack at this position, but resulted almost exclusively in hydroxylation/dehydrofluorination. In this way ketone **16** was formed, and was subsequently reduced to form compounds **17** and **18**.

A couple of years ago we reported on the biotransformation of cyclooctyl *N*-phenylcarbamate with *B. bassiana*.[7] In agreement with a modified distance model, this compound was hydroxylated both in the 4-*cis*- and 4-*trans*- and also in the 5-*cis*- and 5-*trans* positions relative to the carbamate function. Additionally, the resulting ketones were also isolated. Among the 4-hydroxy products, the *trans*-configured species dominated (2:1) over the *cis* compound.[7]

We were now interested in the biotransformation of *cis*-4-fluorocyclooctyl *N*-phenylcarbamate (**15**). After treatment by the standard procedure, besides 19% of recovered **15**, five products were isolated and identified as the optically active ketone **20** (17%), the 4-hydroxyphenyl carbamate **21** (3.5%), not exhibiting optical rotation, and the three isomeric, optically active fluorohydrins **22** (3%, 38% *ee*), **23** (6%, 68% *ee*), and **24** (4%, 50% *ee*) (Scheme 6).



Scheme 6

Structure Determination

The structures of the products, isolated and purified by repeated column chromatography, were determined spectroscopically. All data for ketone **20** agree with those already found for the main product of biohydroxylation of cyclooctyl *N*-phenylcarbamate,[7] except for the specific optical rotation $[\alpha]_D$, which is much larger in the case of the biotransformation product of compound **15** (vide infra).

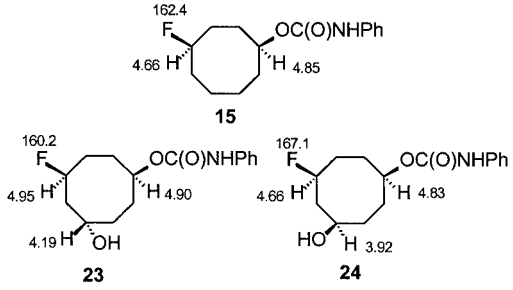
The mass spectrum of the racemic 4-hydroxylated carbamate **21**, besides the molecular ion (m/z = 281) and the fragment corresponding to HF elimination (m/z = 261), shows the typical Biemann shift of all characteristic ions of the carbamate fragmentation of the starting material **15** by 16 mass units. The signals in the NMR spectra of the alicyclic part of the molecule are quite similar to those of **15**. As would be expected, the chemical shifts and the coupling pattern of the aromatic protons, and also the ^{13}C shifts of the *p*-carbons of **15** and **21**, are significantly different (123.1 versus 153.6 ppm).

The mass spectra of all isomeric fluorohydrins **22**, **23**, and **24**, besides the molecular ions (m/z = 281) and the fragments corresponding to HF elimination (m/z = 261), contain significant key fragments of the substituted alicyclic part of the molecules (m/z = 145, $C_8H_{14}FO^+$). The IR spec-

tra of all fluorohydrins show characteristic OH and NH group absorptions of between 3400 and 3300 cm^{-1} and C=O frequencies at about 1715 cm^{-1}.

In the ^1H NMR spectrum of compound **22** the signal of the C*H*OH/group is found as a doublet of multiplets at δ = 4.00 ppm ($^3J_{H,F}$ = 22.4 Hz). This significant coupling constant hints at the vicinal arrangement of the substituents. This assumption is supported by the doublets of the C*H*OH and CHF groups found in the proton-decoupled ^{13}C NMR spectrum at δ = 71.6 ppm ($^2J_{C,F}$ = 20.3 Hz) and 95.3 ppm ($^1J_{C,F}$ = 170.4 Hz). A doublet of a doublet of a triplet of the CHF group appears at δ = 4.77 ppm in the ^1H NMR spectrum. As well as the H,F coupling constant (46 Hz), a $^3J_{H,H}$ of about 9 Hz and two $^3J_{H,H}$ of about 3 Hz are found. Homonuclear decoupling with the α-protons of the C*H*OH group simplifies the CHF signal to a doublet of two doublets with $^3J_{H,H}$ = 9.6 Hz and $^3J_{H,H}$ = 3.4 Hz. Consequently, one vicinal coupling of about 3 Hz corresponds to the spin system of C*H*OH and CHF groups and hints at a *cis* arrangement of these protons, so these substituents are also in a *cis* configuration.

The assignment of the regiochemistry and the relative configurations of the fluorohydrins **23** and **24** was more difficult. The ^1H NMR spectrum of compound **23** shows the multiplets of the C*H*OH/ and C*H*OC(O)NHPh groups at δ = 4.19 or 4.90 ppm, respectively. The latter signal is partially overlapped by part of the doublet of the CHF group at δ = 4.95 ppm ($^2J_{H,F}$ = 48 Hz), such an overlap also being observed for the signals at δ = 4.83 ppm [CHOC(O)NHPh] and δ = 4.66 ppm (CHF) of compound **24**. The multiplet of the C*H*OH group appears at δ = 3.92 ppm. From these data and scalar couplings of the protons, it is not possible to determine the position of the OH groups in **23** and **24**. However, corresponding $^1H,^1H$-COSY spectra suggest the 4-position relative to the carbamate function of the hydroxy groups both in **23** and **24**. Comparison of the chemical shifts of the CHF- and C*H*OC(O)NHPh groups of **15** and **24** shows almost no influence from the additional OH group of **24** [δ = 4.66 ppm for the CHF groups in **15** and **24**, and δ = 4.85 ppm or δ = 4.83 ppm for the CHOC(O)NHPh groups of **15** and **24**, respectively]. Thus, all the protons mentioned should be located on the same side of the ring plane, not influencing each other (Scheme 7).



Scheme 7. Characteristic ^1H and ^{19}F NMR chemical shifts of compounds **15**, **23**, and **24**

Controversially, the chemical shifts of the mentioned groups are significantly shifted in compound **23** [δ = 4.95 ppm for CHF, 4.90 ppm for C*H*OC(O)NHPh]. Moreover, the chemical shifts of the C*H*OH groups of **23** (δ = 4.19 ppm) and **24** (δ = 3.92 ppm) are quite different. All together, this suggests that the OH group of **23** is in a *trans* relationship both to the fluorine atom and the carbamate function. Thus, the OH function comes close to the protons discussed and can interact with them, resulting in the observed downfield shift. Moreover, the fluorine substituent approximates to the α-proton to the C*H*OH group, resulting in a significant downfield shift. A similar conclusion can be drawn from the fluorine chemical shifts. While there is only a weak influence of the additional OH-function of **24** (δ = −162.4 ppm for **15** and δ = −160.2 ppm for **24**), a significant high-field shift of δ = 5.4 ppm is observed for **23** (δ = −167.8 ppm). The relative configurations of the substituents in **23** and **24** become more evident from NOE difference spectra. For compound **23**, positive resonances were found only for the methylene groups, which could not be assigned. For compound **24**, in contrast, a significant NOE at the C*H*OH group was observed on irradiation of the CHF frequency and vice versa. Additionally, several signals in the methylene part of the spectra became more intense.

In parallel with the NOE measurements, the most stable conformations of the diastereomeric products **23** and **24** were calculated semiempirically at the AM1 level of theory.[25] For the *cis* compound **24**, a boat-chair conformation, bearing all three substituents in quasiequatorial positions, was calculated to be the most stable. In this conformation the α-protons of the C*H*OH and CHF groups have a separation of 2.6 Å. This comparably close contact seems to be responsible for the observed NOE. For **23**, in contrast, a boat-chair and a crown conformation are almost equal in stability. In both conformers the separations of relevant protons are >3.4 Å. This could explain the absence of any NOEs between α-protons of functional groups.

The enantiomeric excesses of fluorohydrins **22**, **23**, and **24** were determined by ^{19}F NMR spectroscopy after esterification with Mosher's acid[26] (Supporting information, see also the footnote on the first page of this article). The absolute configurations of the fluorohydrins were not determined.

The enantiomeric excess of the ketone (−)-**20** also could not be determined. However, the specific optical rotation ($[\alpha]_D$) is much larger than that of the same compound obtained by biotransformation of cyclooctyl *N*-phenylcarbamate.[7] This reaction also gave, besides the *cis*/*trans* isomeric products hydroxylated in the 5-position and the resulting 5-oxo-product, a 2:1 mixture of *trans*- and *cis*-4-(hydroxy)cyclooctyl *N*-phenylcarbamate and the ketone (−)-**20**. This ketone exhibited a quite low specific optical rotation of $[\alpha]_D^{21} = -1.5$. In this case, compound (−)-**20** can be formed both from *cis*- and from *trans*-4-hydroxycyclooctyl *N*-phenylcarbamates. This was shown for the products of the biotransformation of *trans*-2-fluorocycloheptyl *N*-phenylcarbamate and subsequent Jones oxidation of the

formed (*R*,*R*,*R*)-(+)-4-hydroxycycloheptyl *N*-phenylcarbamate.[8a,8b] The optical rotation of (−)-**20** is much larger ($[\alpha]_D^{21} = -12.2$) for the compound isolated from the biohydroxylation of racemic *cis*-4-fluorocyclooctyl *N*-phenylcarbamate (**15**). Thus, a rather efficient racemate cleavage must have occurred in biotransformation of compound **15**.

Therefore, all positions hydroxylated in the biotransformation of the parent cyclooctyl *N*-phenylcarbamate[7] were also hydroxylated in the case of the fluorinated derivative **15**. In contrast to 4-oxocyclohexyl *N*-phenylcarbamate (**16**), the main product of biotransformation of the 4-fluoro carbamate **9**, the main product of the reaction of **15**, the ketone (−)-**20**, was not reduced to the corresponding alcohols.

Conclusion

Fluorine substitution of a hydrocarbon position that is hydroxylated by *B. bassiana* in the nonfluorinated parent compounds does not necessarily prevent oxygenation in the positions geminal or vicinal to the fluorine substituent. Examples of such so-called blocking fluorination have been observed with other microorganisms[9−12] and in the biotransformation of 5-fluoro-nortricyclan-3-yl *N*-phenylcarbamates with *B. bassiana*.[4] In contrast, biotransformation of 4-*cis*-fluorocycloalkyl *N*-phenylcarbamates **9** and **15** resulted in hydroxylation of all positions that were also attacked in the corresponding parent compounds. Hydroxylation of the fluoromethine groups most probably produces geminal fluorohydrins, which are not stable and are subsequently dehydrofluorinated to give the corresponding ketones **16** or (−)-**20**, the corresponding main products of the microbial transformation.

Experimental Section

General Remarks: IR spectra were recorded on neat compounds (film or in KBr), or highly diluted in dry CCl_4, with a Nicolet 5DXC-FT IR spectrometer. ^{1}H NMR (300.1 MHz), ^{13}C NMR (75.5 MHz), and ^{19}F NMR spectra (282.3 MHz) were recorded with ca. 20% solutions in $CDCl_3$ with a Bruker WM 300 spectrometer. Chemical shifts are reported as δ values [ppm] relative to TMS (^{1}H and ^{13}C) or $CFCl_3$ (^{19}F), respectively, as internal standards. The multiplicities of ^{13}C signals were determined by the DEPT operation. Mass spectra (electron impact ionization, 70 eV) were recorded by GC/MS coupling, Varian GC 3400/MAT and data system of Finnigan/MAT. The product ratios of microbial transformations were determined on the crude product mixtures by ^{19}F NMR spectroscopy or gas chromatography. The products were separated by column chromatography (silica gel, Merck 60, 70−230 mesh, diethyl ether/pentane, 1:1). Optical rotations were determined with a Perkin−Elmer 241 polarimeter. Microanalyses were carried out by the Microanalytical Laboratory, Organic Chemistry Institute, University of Münster, on a Foss Heraeus CHN-O analyzer.

Synthesis of *cis*-4-Fluorocyclohexyl *N*-Phenylcarbamate (9)

***cis/trans*-4-Fluorocyclohexyl Acetates (3 and 4):** $RhCl_3$ (140 mg, 0.64 mmol) and Aliquat 336 (270 mg, 0.67 mmol) were added to a solution of 4-fluorophenyl acetate (1.54 g, 10 mmol) in dichloroethane (10 mL) in a hydrogenation apparatus. The apparatus was flushed first with argon to remove oxygen and then several times with hydrogen. The mixture was stirred for 3 d under hydrogen at atmospheric pressure, and water (25 mL) was then added. The phases were separated and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic layer was dried over $MgSO_4$ and filtered through 10 g of silica gel. The solvent was evaporated to give a colorless liquid. Yield: 1.359 g of a colorless liquid containing 60% (GC) of unchanged starting compound **2**, and 40% of a 10:1:7 mixture of the saturated acetates **3**, **4**, and **6**. This mixture was not separated, but was applied in the next step for hydrolysis after investigation by GC/MS.

***cis*-1-Acetoxy-4-fluorocyclohexane (3):** MS (GC/MS): *m*/*z* (%) = 159 (0.4) [$M^+ - 1$], 140 (2) [$M^+ - HF$], 117 (4) [$M^+ - CH_3CO$], 100 (7), 98 (9), 97 (4), 81 (10), 80 (51), 79 (5), 61 (4), 55 (6), 54 (12), 44 (3), 43 (100), 41 (7).

***trans*-1-Acetoxy-4-fluorocyclohexane (4):** MS (GC/MS): *m*/*z* (%) = 118 (8), 117 (22) [$M^+ - CH_3CO$], 100 (15), 98 (16), 97 (2), 81 (14), 80 (100), 79 (17), 61 (22), 55 (13), 54 (26), 43 (100), 41 (23).

***cis/trans*-4-Fluorocyclohexanols (6 and 7):** The mixture of **3**, **4**, and **5** prepared above was dissolved in methanol (40 mL), and KOH (986 mg, 18 mmol) was added. The solution was stirred at room temperature for 3 h. The methanol was evaporated, and the residue was dissolved in dichloromethane (30 mL) and washed with water (2 × 15 mL). The organic layer was dried over $MgSO_4$, and the solvent was evaporated. Gas chromatographic analysis showed a 10:1:7 mixture of **6**, **7**, and cyclohexanol. The fluorohydrins **6** and **7** were separated from cyclohexanol by column chromatography (silica gel, pentane/diethyl ether, 1:1). Yield: 207 mg (18%, in relation to **2**). The fluorohydrins **6** and **7** could not be separated even by HPLC. ^{1}H NMR: δ = 1.32−1.78 (m, 6 H, $-CH_2$ [**6**], $-CH_2$ [**7**]), 1.89−2.10 (m, 2 H, $-CH_2$ [**6**], $-CH_2$ [**7**]), 3.59−3.72 (m, 1 H, 1−CH [**6**]), 3.73−3.82 (m, 1 H, 1-H [**7**]), 4.58 (dm, $^2J_{H,F}$ = 48.9 Hz, 1 H, 4-H [**7**]), 4.64 (dsept, $^2J_{H,F}$ = 48.4, $^3J_{H,H}$ = 2.71 Hz, 1 H, 4-H [**6**]) ppm. ^{13}C NMR: δ = 28.3 (dt, C-2, C-6 [**7**]), 28.6 (ddt, $^2J_{C,F}$ = 20.4 Hz, C-3, C-5 [**6**]), 29.9 (d, C-2, C-6 [**6**]), 30.5 (ddt, $^2J_{C,F}$ = 7.6 Hz, C-3, C-5 [**7**]), 68.0 (d, C-1 [**7**]), 68.2 (d, C-1 [**6**]), 88.4 (dd, $^1J_{C,F}$ = 170.4 Hz, C-4 [**6**]), 90.5 (dd, $^1J_{C,F}$ = 170.4 Hz, C-4 [**7**]) ppm. ^{19}F NMR: δ = −181.2 (m, 4-F [**6**]), −179.6 (m, 4-CF, [**7**]) ppm. MS (GC/MS) of compound **6**: *m*/*z* (%) = 118 (11) [M^+], 98 (28) [$M^+ - HF$], 83 (38), 80 (24), 70 (23), 59 (9), 57 (100), 55 (68), 43 (17), 41 (45), 39 (14). MS (GC/MS) of compound **7**: *m*/*z* (%) = 118 (5) [M^+], 98 (23) [$M^+ - HF$], 83 (15), 80 (18), 70 (17), 59 (13), 57 (100), 55 (50), 43 (26), 41 (31), 39 (29).

***cis*- and *trans*-4-Fluorocyclohexyl *N*-Phenylcarbamates (9 and 10):** The 10:1 mixture of **6** and **7** (472 mg, 4 mmol), on treatment with phenyl isocyanate (571 mg, 4.8 mmol) and heating at reflux in petroleum ether (110−140 °C) according to ref.[8] gave a 10:1 mixture of the carbamates **9** and **10**. Yield: 730 mg (77%). Pure *cis*-4-fluorocyclohexyl *N*-phenylcarbamate (**9**) was obtained after several crystallizations from petroleum ether. Yield: 548 mg (56%).

***cis*-4-Fluorocyclohexyl *N*-Phenylcarbamate (9):** ^{1}H NMR: δ = 1.54−2.09 (m, 8 H, 2-H_2, 3-H_2, 5-H_2, 6-H_2), 4.69 (dm, $^2J_{H,F}$ = 48.9, $^3J_{H,H}$ = 2.9 Hz, 1 H, 4-H), 4.72−4.85 (m, 1 H, 1-H), 6.61 (br. s, 1 H, NH), 7.04 (tt, $^3J_{H,H}$ = 7.2, $^4J_{H,H}$ = 1.3 Hz, 1 H, *p*-CH), 7.29 (tt, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.9 Hz, 2 H, *m*-CH), 7.37 (dd, $^3J_{H,H}$ = 8.6,

$^4J_{H,H}$ = 1.0 Hz, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 26.8 (dt, $^3J_{C,F}$ = 5.1 Hz, C-2, C-6), 28.6 (dt, $^2J_{C,F}$ = 20.4 Hz, C-3, C-5), 71.3 (d, C-1), 88.4 (dd, $^1J_{C,F}$ = 170.4 Hz, C-4), 118.7 (d, *o*-C), 123.4 (d, *p*-C), 129.0 (d, *m*-C), 137.9 (s, *ipso*-C), 153.0 (s, C=O) ppm. ^{19}F NMR: δ = −180.4 (m, 4-F) ppm. MS (GC/MS, Ion Trap): *m*/*z* (%) = 237 (6) [M$^+$], 236 (52) [M$^+$ − 1], 150 (2), 137 (50) [$C_6H_5NHCO_2H^+$], 132 (14), 119 (5), 106 (2), 93 (100) [$C_6H_5NH_2^+$], 81 (55), 65 (18), 59 (12), 39 (36). IR (Film): ṽ = 3402, 3318 (m, ν −CONH), 2947 (m, ν C−H), 1698 (s, ν C=O), 1601 (m, δ N−H), 1532, 1443, 1316 (m, δ C−H), 1219 (s, δ C−F), 1057, 938. $C_{13}H_{16}FNO_2$ (237.27): calcd. C 65.81, H 6.80, N 5.90; found C 65.82, H 6.97, N 6.04.

***trans*-4-Fluorocyclohexyl *N*-Phenylcarbamate (10):** This compound was not isolated in pure form. The spectroscopic data were taken from the spectra of an enriched sample. ^{1}H NMR: δ = 1.48−2.15 (m, 8 H, −CH_2), 4.72−4.94 (m, 2 H, 1-H, 4-H), 6.55 (br. s, 1 H, NH), 7.04 (tt, $^3J_{H,H}$ = 7.3, $^4J_{H,H}$ = 1.3 Hz, 1 H, *p*-CH), 7.29 (m, 2 H, *m*-CH), 7.36 (m, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 26.6 (dt, $^3J_{C,F}$ = 5.1 Hz, C-2, C-6), 27.8 (dt, $^2J_{C,F}$ = 20.4 Hz, C-3, C-5), 71.2 (d, C-1), 89.5 (dd, $^1J_{C,F}$ = 170.4 Hz, C-4), 118.7 (d, *o*-C), 123.4 (d, *p*-C), 129.0 (d, *m*-C), 137.9 (s, *ipso*-C), 153.0 (s, C=O) ppm. ^{19}F NMR: δ = −181.8 (m, 4-F) ppm. MS (GC/MS): *m*/*z* (%) = 237 (25) [M$^+$], 150 (3), 137 (36), 137 (69) [$C_6H_5NHCO_2H^+$], 132 (17), 119 (27), 101 (7), 93 (100) [$C_6H_5NH_2^+$], 81 (80), 59 (16), 55 (24), 41 (30).

Synthesis of *cis*-4-Fluorocyclooctyl *N*-Phenylcarbamate (15)

Ring Opening of Cyclooctene Oxide (11) by Treatment with Olah's Reagent: Olah's reagent (Py·9HF, 7.4 g, 280 mmol) in dichloromethane (10 mL) was cooled to −15 °C in a Teflon round-bottomed flask with a Teflon-covered stirring bar. A solution of cyclooctene oxide (**11**, 12.6 g, 100 mmol) in dichloromethane (15 mL) was added dropwise to this mixture over 30 min, whilst stirring at this temperature. After 3 h the solution was warmed up to room temperature and stirring at this temperature was continued for 20 h. Concentrated, ice-cold ammonia solution was then added with stirring until a pH of about 7 was reached. The phases were separated, and the aqueous phase was extracted with dichloromethane (2 × 20 mL). The combined organic layer was washed with 5% $NaHCO_3$ solution (20 mL) and water (2 × 20 mL). After the mixture had been dried over $MgSO_4$, the solvent was evaporated to give 8.1 g of a 5:60:30 mixture of **12**, **13**, and **14** besides some traces of other products, which were not identified. This mixture was distilled carefully over a 10 cm Vigreux column.

***cis*-4-Fluorocyclooctanol (13):** Yield: 5.1 g (35%). B.p. 113−115 °C (7 Torr); m.p. 27−30 °C. ^{1}H NMR (400 MHz): δ = 1.40−1.44 (m, 3 H), 1.60−1.80 (m, 10 H), 4.60 (dm, 1 H, $^2J_{H,F}$ = 45.6 Hz, −CHF), 3.75 (m, 1 H, −C*H*OH) ppm. ^{13}C NMR: δ = 21.4 (d, $^3J_{C,F}$ = 10.2 Hz, C-6), 21.7 (s, C-7), 28.0 (d, $^2J_{C,F}$ = 22.9 Hz, C-3), 29.3 (d, $^3J_{C,F}$ = 7.6 Hz, C-2), 30.3 (d, $^2J_{C,F}$ = 20.3 Hz, C-5), 32.9 (s, C-8), 71.1 (s, C-4), 93.6 (d, $^1J_{C,F}$ = 162.7 Hz, C-1) ppm. ^{19}F NMR: δ = −161.2 (m, 4-F) ppm. IR (CCl_4): ṽ = 3621 (m, ν OH_{free}), 3353 (br. s, ν OH_{ass}). MS (GC/MS): *m*/*z* (%) = 146 (5) [M$^+$], 126 (10) [M − HF], 109 (25), 97 (20), 82 (70), 67 (100), 57 (60), 54 (70). $C_8H_{15}FO$ (146.2): calcd. C 65.72, H 10.34; found C 65.53, H 10.30.

***cis*-4-Fluorocyclooctyl *N*-Phenylcarbamate (15):** The fluorohydrin **13** (3.60 g, 25 mmol) was heated at reflux with phenyl isocyanate (3.60 g, 30 mmol) in petroleum ether (110−140 °C) according to ref.[8], to give **15** after recrystallization from the same solvent. Yield: 5.30 g (81%). M.p. 58−60 °C (petroleum ether). ^{1}H NMR: δ = 1.42−1.53 (m, 2 H, −CH_2), 1.70−2.07 (m, 10 H, −CH_2,), 4.66 (dm, $^3J_{H,F}$ = 45.5 Hz, 1 H, CHF), 4.85 (m, 1 H, CHOCO), 6.77 (br. s, 1 H, NH), 7.03 (t, $^3J_{H,H}$ = 7.4 Hz, 1 H, *p*-CH), 7.27 (t, $^3J_{H,H}$ = 7.9 Hz, 2 H, *m*-CH), 7.37 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 21.3 (d, $^3J_{C,F}$ = 7.6 Hz, C-2), 22.5 (s, C-7), 26.6 (d, $^3J_{C,F}$ = 7.6 Hz, C-6), 28.1 (s, $^2J_{C,F}$ = 22.9 Hz, C-3), 30.2 (s, C-8), 30.9 (d, $^2J_{C,F}$ = 22.9 Hz, C-5), 75.1 (s, C-1), 93.4 (d, $^2J_{C,F}$ = 165.3 Hz, C-4), 118.6 (s, *o*-C), 123.3 (s, *p*-C), 129.0 (s, *m*-C), 138.0 (s, *ipso*-C), 152.9 (s, C=O) ppm. ^{19}F NMR: δ = −162.4 (m) ppm. MS (GC/MS): *m*/*z* (%) = 265 (25) [M$^+$ − HF], 137 (62), 120 (12), 119 (15), 109 (55), 93 (100), 81 (18), 67 (78). IR (CCl_4): ν = 3324 (br. s, ν −NH), 3150 (s, ν −CH), 2868 (w, ν −CH), 1700 (br. s, ν −C=O), 1610 (s), 1542 (s), 1410 (s), 1223 (w), 1068 (w). $C_{15}H_{20}FO_2N$ (265.3): calcd. C 67.90, H 7.60, N 5.28; found C 68.06, H 7.86, N 5.28.

Biotransformation with *Beauveria bassiana* ATCC 7159

The corresponding *N*-phenylcarbamates **9** and **15** (300 mg each) were transformed with a growing culture of *B. bassiana* ATCC 7159 by the procedure described in ref.[8]

Transformation of *cis*-4-Fluorocyclohexyl *N*-Phenylcarbamate (9): Together with some starting material **9** (60 mg, 20%), four products, **16** to **19**, were isolated by repeated column chromatography and HPLC in about 32% combined yield.

4-Oxocyclohexyl *N*-Phenylcarbamate (16): Yield: 36 mg (12.6%). M.p. 134−135 °C ($CHCl_3$). ^{1}H NMR: δ = 2.03−2.18 (m, 4 H, 2-H_2, 6-H_2), 2.29−2.44 (m, 2 H, 3-H_2, 5-H_2), 2.46−2.62 (m, 2 H, 3-H_2, 5-H_2), 5.17 (q, $^3J_{H,H}$ = 5.1 Hz or 4.6 Hz, 1 H, 1-H), 6.66 (br. s, 1 H, NH), 7.06 (tt, $^3J_{H,H}$ = 7.3, $^4J_{H,H}$ = 1.3 Hz, 1 H, *p*-CH), 7.27 (tt, $^3J_{H,H}$ = 8.7, $^4J_{H,H}$ = 1.7 Hz, 2 H, *m*-CH), 7.34 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 30.6 (t, C-2, C-6), 37.2 (t, C-3, C-5), 69.6 (d, C-1), 118.9 (d, *o*-C), 123.7 (d, *p*-C), 129.1 (d, *m*-C), 137.7 (s, *ipso*-C-8), 152.8 (s, C=O), 209.7 (s, C-4) ppm. MS (GC/MS, Ion-Trap): *m*/*z* (%) = 233 (3) [M$^+$], 232 (41) [M$^+$ − 1], 137 (43) [$C_6H_5NHCO_2H^+$], 119 (8), 106 (1), 93 (100) [$C_6H_5NH_2^+$], 77 (12), 69 (29), 55 (25), 41 (63) [$C_3H_5^+$]. IR (Film): ṽ = 3440, 3290 (s, ν −CONH), 3141 (w, ν C−$H_{arom.}$), 2942 (w, ν C−H_2), 1713 (s, ν C=O), 1607, 1558 (s, ν N−H), 1451, 1323 (m, δ C−H), 1238 (s, δ C−O), 1068, 769 (m, δ C−H_{arom}). High-resolution MS: $C_{13}H_{15}NO_3$: calcd. 233.10519; found 233.10445.

4-Hydroxycyclohexyl *N*-Phenylcarbamates (17 and 18): ^{1}H NMR: δ = 1.32−2.13 (m, 8 H,-CH_2), 3.65−3.84 (m, 1 H, 4-H), 4.65−4.91 (m, 1 H, 1-H), 6.68 (br. s, 1 H, NH [**17**] or [**18**]), 6.82 (br. s, 1 H, NH [**18**] or [**17**]), 7.02 (tt, $^3J_{H,H}$ = 7.2, $^4J_{H,H}$ = 1.3 Hz, 1 H, 11-H), 7.27 (tt, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 2.0 Hz, 2 H, 10-CH, 12-H), 7.34 (dd, $^3J_{H,H}$ = 8.6, $^4J_{H,H}$ = 1.1 Hz, 2 H, 9-H, 13-H) ppm. ^{13}C NMR: δ = 27.5 (t, C-2, C-6) [**17**] or [**18**], 28.8 (t, C-2, C-6) [**17**] or [**18**], 30.5 (t, C-3, C-5) [**17**] or [**18**], 32.2 (t, C-3, C-5) [**17**] or [**18**], 67.7 (d, C-4) [**17**] or [**18**], 68.5 (d, C-4) [**17**] or [**18**], 70.8 (d, C-1) [**17**] or [**18**], 72.7 (d, C-1) [**17**] or [**18**], 118.7 (d, *o*-C [**17**] and [**18**]), 123.2 (d, *p*-C [**17**] and [**18**]), 129.0 (d, *m*-C [**17**] and [**18**]), 138.0 (s, *ipso*-C [**17**] and [**18**]), 153.1 (s, C=O [**17**] and [**18**]) ppm. MS (GC/MS, Ion Trap) [**17, 18**]: *m*/*z* (%) = 235 (3) [M$^+$], 234 (28) [M$^+$ − 1], 137 (40) [$C_6H_5NHCO_2H^+$], 119 (15), 106 (3), 93 (100) [$C_6H_5NH_2^+$], 81 (62), 77 (13), 65 (20), 55 (18), 39 (35). IR (Film): ṽ = 3397 (s, ν O−H), 3127 (m, ν −CONH), 3070 (w, ν C−$H_{arom.}$), 2942 (m, ν C−H_2), 1700 (s, ν C=O), 1600, 1543 (s, ν N−H), 1437, 1323 (m, δ C−H), 1238 (s, δ C−O), 1060, 748 (m, δ C−H_{arom}).

***cis*-4-Fluorocyclohexyl *N*-(4-Hydroxyphenyl)carbamate (19):** Yield: Traces. MS (GC/MS, Ion-Trap): *m*/*z* (%) = 253 (4) [M$^+$], 252 (13) [M$^+$ − 1], 207 (1), 152 (40) [*p*-(OH)$C_6H_4NHCO_2^+$], 135 (12), 119 (3), 109 (100) [*p*-(OH)$C_6H_4NH_2^+$], 93 (100) [$C_6H_4OH^+$], 81 (62), 77 (13), 65 (20), 55 (18), 39 (35).

Transformation of *cis*-4-Fluorocyclooctyl *N*-Phenylcarbamate (15): Together with the starting material (229 mg, 19%), five products, **20** to **24**, were isolated from three batches (300 mg of **15** each) of transformation product by repeated column chromatography and HPLC.

(−)-4-Oxocyclooctyl *N*-Phenylcarbamate (20): Yield: 162 mg (17%). M.p. 90−92 °C (petroleum ether). $[\alpha]_{589}^{20} = -12.2$, $[\alpha]_{578}^{20} = -13.0$, $[\alpha]_{546}^{20} = -15.0$, $[\alpha]_{536}^{20} = -26.1$ (c = 0.2, $CHCl_3$). ^{1}H NMR (CD_3OD): δ = 1.07−1.18 (m, 1 H, $-CH_2$), 1.47−1.78 (m, 5 H, $-CH_2$), 2.08−2.50 (m, 6 H, $-CH_2$), 4.76 (sept, 1 H, CHOCO), 6.90 (t, $^3J_{H,H}$ = 7.4 Hz, 1 H, *p*-CH), 7.15 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, *m*-CH), 7.30 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 22.6 (s), 28.0 (s), 28.4 (s), 30.6 (s), 39.0 (s), 40.6 (s), 74.3 (s, C-1), 118.6 (s, *o*-C), 120.9 (s, *p*-C), 129.1 (s, *m*-C), 137.8 (s, *ipso*-C), 152.8 (s, C=O), 216.4 (s, C-4) ppm. MS (GC/MS): *m*/*z* (%) = 261 (24) [M^+], 142 (18), 137 (22), 120 (12), 119 (85), 107 (16), 93 (58), 91 (53), 83 (21), 77 (18), 55 (100). FT-IR (KBr): $\tilde{\nu}$ = 3321 (br. s, ν −NH), 2939 (s, ν −CH), 2863 (s, ν −CH), 1727 (br. s, ν C=O, δ −NH), 1699 (br. s, ν C=O), 1600 (m), 1551 (s), 1501 (w), 1444 (m), 1315 (m), 1222 (s), 1051 (m). High resolution MS: $C_{15}H_{19}O_3NF$ (263.3). calcd. 279.1709 (for $C_{15}H_{19}O_3NF + NH_4^+$); found 279.1707.

***cis*-4-Fluorooctyl *N*-(4-Hydroxyphenyl)carbamate (21):** Yield: 37 mg (3.5%). ^{1}H NMR: δ = 1.41−2.08 (m, 12 H, $-CH_2$), 4.62 (d sept, $^2J_{H,F}$ = 45.8 Hz, 1 H, CHF), 4.84 (m, 1 H, CHOCO), 4.96 (s, 1 H, OH), 6.39 (br. s, 1 H, NH), 6.76 (d t, $^3J_{H,H}$ = 9.1 Hz, 2 H, *m*-CH), 7.2 $^3J_{H,H}$ = 8.6 Hz, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 21.3 (d, $^3J_{C,F}$ = 7.6 Hz, C-2), 22.5 (s, C-7), 26.6 (d, $^3J_{C,F}$ = 7.6 Hz, C-6), 28.1 (s, $^2J_{C,F}$ = 22.9 Hz, C-3), 30.2 (s, C-8), 30.9 (d, $^2J_{C,F}$ = 22.9 Hz, C-5), 75.1 (s, C-1), 93.4 (d, $^2J_{C,F}$ = 165.3 Hz, C-4), 115.8 (s, *o*-C), 121.2 (s, *m*-C), 130.9 (s, *ipso*-C), 152.1 (s, C=O), 153.6 (s, *p*-C) ppm. ^{19}F NMR: δ = −162.3 (m) ppm. MS (GC/MS): *m*/*z* (%) = 281 (18) [M^+], 261 (5) [M^+ − HF], 153 (85), 135 (18), 109 (100), 81 (30), 67 (69), 55 (24). FT-IR (KBr): $\tilde{\nu}$ = 3392 (br. s, ν −NH, ν −OH), 3317 (br. s, ν −NH, ν −OH), 2941 (s, ν −CH), 2871 (w, ν −CH), 1701 (s, ν C=O, δ −NH), 1545 (s), 1522 (s), 1441 (m), 1232 (s), 1053 (m). High-resolution MS: $C_{15}H_{20}O_3NF$ (281.3): calcd. 299.1771 (for $C_{15}H_{20}O_3NF + NH_4^+$); found 299.1790.

(+)-*c*-4-Fluoro-*c*-5-hydroxycyclooct-*r*-1-yl *N*-Phenylcarbamate (22): Yield: 31 mg (3%). M.p. 120 °C (petroleum ether). $[\alpha]_{589}^{21} = +1.2$ (c = 0.1, $CHCl_3$). ^{1}H NMR: δ = 1.53−2.39 (m, 11 H, $-CH_2$, −OH), 4.00 (dd, $^3J_{C,F}$ = 22.4 Hz, 1 H, C*H*OH), 4.77 (ddt, $^2J_{H,F}$ = 45.9 Hz, 1 H, CHF), 4.91 (m, 1 H, CHOCO), 6.59 (br. s, 1 H, −NH), 7.06 (t, $^3J_{H,H}$ = 7.2 Hz, 1 H, *p*-CH), 7.30 (t, $^3J_{H,H}$ = 7.9 Hz, 2 H, *m*-CH), 7.36 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 18.2 (s, C-7), 24.4 (s, $^2J_{C,F}$ = 22.9 Hz, C-3), 27.5 (s, $^3J_{C,F}$ = 7.6 Hz, C-2 or C-6), 29.9 (d, $^3J_{C,F}$ = 7.6 Hz, C-2 or C-6), 31.8 (s, C-8), 71.6 (s, $^2J_{C,F}$ = 20.3 Hz, C-5), 73.6 (s, C-1), 95.3 (s, $^1J_{C,F}$ = 170.4 Hz, C-4), 118.6 (s, *o*-C), 123.4 (s, *p*-C), 129.1 (s, *m*-C), 137.8 (s, *ipso*-C), 152.8 (s, C=O) ppm. ^{19}F NMR: δ = −171.9 (m) ppm. MS (GC/MS): *m*/*z* (%) = 281 (38) [M^+], 261 (8) [M^+ − HF], 145 (6), 137 (79), 120 (28), 119 (98), 107 (18), 93 (100), 91 (42), 77 (18), 55 (64). FT-IR (KBr): $\tilde{\nu}$ = 3416 (br. s, ν −OH, ν −NH), 3317 (br. s, ν −OH, ν −NH), 2944 (s, ν −CH), 2882 (w, ν −CH), 1714 (s, ν C=O), 1609 (m), 1329 (m), 1447 (m), 1329 (w), 1236 (m). High-resolution MS: $C_{15}H_{20}FNO_3$ (281.3). calcd. 299.1771 (for $C_{15}H_{20}FNO_3 + NH_4^+$); found 299.1733.

(−)-*c*-4-Fluoro-*t*-6-hydroxycyclooct-*r*-1-yl *N*-Phenylcarbamate (23): Yield: 62 mg (6%). $[\alpha]_{589}^{20} = -11.8$, $[\alpha]_{578}^{20} = -12.4$, $[\alpha]_{546}^{20} = -13.9$, $[\alpha]_{536}^{20} = -23.6$ (c = 0.21, $CHCl_3$). ^{1}H NMR: δ = 1.55−2.20 (m, 11 H, $-CH_2$, −OH), 4.19 (m, 1 H, CHOH), 4.90 (m, 1.5 H, CHF, CHOCO), 4.9 (m, 0.5 H, CHF), 6.59 (br. s, 1 H, −NH), 7.06 (t, $^3J_{H,H}$ = 7.2 Hz, 1 H, *p*-CH), 7.30 (t, $^3J_{H,H}$ = 7.9 Hz, 2 H, *m*-CH), 7.36 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 26.3 (d, $^3J_{C,F}$ = 7.4 Hz, C-2), 29.9 (s, C-8), 28.4 (d, $^2J_{C,F}$ = 22.8 Hz, C-3), 30.5 (s, C-7), 39.3 (d, $^2J_{C,F}$ = 22.9 Hz, C-5), 66.5 (d, $^3J_{C,F}$ = 7.6 Hz, C-6), 74.4 (s, C-1), 89.6(d, $^1J_{C,F}$ = 165.3 Hz, C-4), 118.7 (s, *o*-C), 123.5 (s, *p*-C), 129.1 (s, *m*-C), 137.9 (s, *ipso*-C), 152.9 (s, C=O) ppm. ^{19}F NMR: δ = −167.8 (m) ppm. MS (GC/MS): *m*/*z* (%) = 281 (2) [M^+], 145 (15), 137 (28), 120 (20), 119 (19), 107 (21), 93 (100), 79 (61), 65 (24), 55 (41). IR (KBr): $\tilde{\nu}$ = 3400 (br. s, ν −OH, ν −NH), 2935 (s, ν −CH), 2877 (w, ν −CH), 1702 (s, ν C=O, δ −NH), 1604 (m), 1540 (m), 1447 (m), 1324 (m), 1237 (s), 1103 (w). High-resolution MS: $C_{15}H_{20}FNO_3$ (281.3). calcd. 299.1771 (for $C_{14}H_{19}FNO_3 + NH_4^+$); found 299.1735.

***(−)-c*-4-Fluoro-*c*-6-hydroxycyclooct-*r*-1-yl *N*-Phenylcarbamate (24):** Yield: 42 mg (4%). $[\alpha]_{589}^{20} = -2.6$, $[\alpha]_{578}^{20} = -3.1$, $[\alpha]_{546}^{20} = -4.0$, $[\alpha]_{536}^{20} = -5.7$ (c = 0.7, $CHCl_3$). ^{1}H NMR: δ = 1.52 (br. s, 1 H, OH), 1.69−2.27 (m, 10 H, $-CH_2$), 3.92 (m, 1 H, C*H*OH), 4.66 (m, 0.5 H, CHF), 4.83 (m, 1.5 H, CHF, CHOCO), 6.50 (b. s, 1 H, NH), 7.06 (t, $^3J_{H,H}$ = 7.2 Hz, 1 H, *p*-CH), 7.3 (t, $^3J_{H,H}$ = 7.9 Hz, 2 H, *m*-CH), 7.36 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, *o*-CH) ppm. ^{13}C NMR: δ = 26.4 (d, $^3J_{C,F}$ = 7.6 Hz, C-2), 26.8 (s, C-8), 28.7 (d, $^2J_{C,F}$ = 22.8 Hz, C-3), 30.7 (s, C-7), 39.7 (d, $^2J_{C,F}$ = 20.4 Hz, C-5), 68.0 (d, $^3J_{C,F}$ = 12.7 Hz, C-6), 74.5 (s, C-1), 90.6 (d, $^1J_{C,F}$ = 165.3 Hz, C-4), 118.7 (s, *o*-C), 123.5 (s, *p*-C), 129.1 (s, *m*-C), 137.8 (s, *ipso*-C), 152.8 (s, C=O) ppm. ^{19}F NMR: δ = −160.2 (m) ppm. GC/MS: *m*/*z* (%) = 281 (38) [M^+], 137 (78), 120 (12), 119 (28), 107 (14), 93 (100), 91 (8), 81 (24), 55 (51). IR (KBr): $\tilde{\nu}$ = 3401 (br. s, ν −OH, ν −NH), 2960 (s, ν −CH), 2872 (w, ν −CH), 1705 (m, ν C=O), 1601 (m), 1543 (w), 1444 (w), 1229 (m). High-resolution MS: $C_{15}H_{20}FNO_3$ (281.3). calcd. 281.14271 (for $C_{15}H_{20}FNO_3 + NH_4^+$); found 281.14346.

Preparation of Mosher's Esters: Mosher esters of the alcohols (+)-**22**, (−)-**23**, and (−)-**24** were synthesized in analogy to a procedure[27] originally discovered by Steglich and Höfle (For details see Supporting Information; see also footnote on the first page of this article).

X-ray Crystallographic Study

***cis*-4-Fluorocyclohexyl *N*-Phenylcarbamate (9):** Formula $C_{13}H_{16}FNO_2$, M = 237.27, colorless crystal 0.30 × 0.15 × 0.10 mm, a = 5.231(2), b = 37.826(9), c = 6.504(2) Å, β = 111.71(2)°, V = 1195.6(7) Å^3, $\rho_{calcd.}$ = 1.318 g cm^{-3}, μ = 8.22 cm^{-1}, empirical absorption correction via ψ scan data (0.791 ≤ T ≤ 0.922), Z = 4, monoclinic, space group $P2_1/n$ (No. 14), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 2690 reflections collected ($-h$, $+k$, $\pm l$), [(sinθ)/λ] = 0.62 Å^{-1}, 2433 independent (R_{int} = 0.036) and 1843 observed reflections [$I \geq 2\,\sigma(I)$], 158 refined parameters, R = 0.054, wR^2 = 0.150, max. residual electron density 0.44 (−0.28) e·Å^{-3}, hydrogen at N8 from difference Fourier calculation, others calculated and all refined as riding atoms. ***cis*-4-Fluorocyclooctyl *N*-Phenylcarbamate (15):** Formula $C_{15}H_{20}FNO_2$, M = 265.32, colorless crystal 0.15 × 0.15 × 0.10 mm, a = 5.204(1), b = 18.171(3), c = 7.647(2) Å, β = 109.53(2)°, V = 681.5(2) Å^3, $\rho_{calcd.}$ = 1.293 g cm^{-3}, μ = 7.75 cm^{-1}, empirical absorption correction via ψ scan data (0.893 ≤ T ≤ 0.927), Z = 2, monoclinic, space group $P2_1$ (No. 4), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 1602 reflections collected ($-h$, $+k$, $\pm l$), [(sinθ)/λ] = 0.62 Å^{-1}, 1450 independent (R_{int} = 0.057) and 1058 observed reflections [$I \geq 2\,\sigma(I)$], 173 refined parameters, R = 0.057, wR^2 = 0.145, Flack parameter −0.2(5), max. residual electron density 0.33 (−0.29) e·Å^{-3}, hydro-

gen at N10 from difference Fourier calculation, others calculated and all refined as riding atoms.

4-Oxocyclohexyl *N*-Phenylcarbamate (16): Formula $C_{13}H_{15}NO_3$, M = 233.26, colorless crystal 0.50 × 0.35 × 0.25 mm, a = 7.641(1), b = 12.380(1), c = 12.418(1) Å, β = 94.88(1)°, V = 1170.4(2) Å^3, $\rho_{calcd.}$ = 1.324 g cm^{-3}, μ = 0.94 cm^{-1}, empirical absorption correction via SORTAV (0.954 ≤ T ≤ 0.977), Z = 4, monoclinic, space group $P2_1/n$ (No. 14), λ = 0.71073 Å, T = 198 K, ω scans, 8640 reflections collected (±h, ±k, ±l), [(sinθ)/λ] = 0.71 Å^{-1}, 3505 independent (R_{int} = 0.033) and 3187 observed reflections [$I \geq 2\ \sigma(I)$], 157 refined parameters, R = 0.041, wR^2 = 0.108, max. residual electron density 0.33 (−0.20) e·Å^{-3}, hydrogen at N8 from difference Fourier calculation, others calculated and all refined as riding atoms.

***cis*-4-Hydroxycyclohexyl *N*-Phenylcarbamate (17):** Empirical formula $C_{13}H_{17}NO_3$, M = 235.28, colorless crystal 0.10 × 0.10 × 0.05 mm, a = 5.979(2), b = 13.065(3), c = 16.356(4) Å, β = 98.80(2)°, V = 1262.6(6) Å^3, $\rho_{calcd.}$ = 1.238 g cm^{-3}, μ = 7.18 cm^{-1}, empirical absorption correction via ψ scan data (0.932 ≤ T ≤ 0.965), Z = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 1.54178 Å, T = 223 K, ω/2θ scans, 2666 reflections collected (±h, −k, +l), [(sinθ)/λ] = 0.62 Å^{-1}, 2576 independent (R_{int} = 0.030) and 1302 observed reflections [$I \geq 2\ \sigma(I)$], 158 refined parameters, R = 0.049, wR^2 = 0.107, max. residual electron density 0.17 (−0.19) e·Å^{-3}, hydrogen at N8 from difference Fourier calculation, others calculated and all refined as riding atoms.

CCDC-197805, CCDC-197807, CCDC-197808, and CCDC-197809 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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