Blocking Fluorine Substitution in Biotransformation of Nortricyclanyl *N*-Phenylcarbamates with *Beauveria bassiana*

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The biotransformation of tricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-phenylcarbamate (**8**) by a standard procedure using *Beauveria bassiana* gave a 7:1 mixture of optically active *exo,exo*- and *exo,endo*-5-hydroxytricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-phenylcarbamates **15** and **16** in 19% isolated yield. No ring opening of the three-membered ring was observed. Substitution with a fluorine atom at the 5-*endo*- or 5-*exo*-position prevented hydroxylation of any alicyclic position of the molecules, *p*-hydroxylation of the aromatic ring occurring to a small extent instead.

Introduction

Selective oxygenation of chemically non-activated hydrocarbon positions still remains a problem in synthesis. Microbiological hydroxylation involving monooxygenases is one way to overcome this drawback,[1] one of the most frequently used microorganisms for this purpose being *Beauveria bassiana*. The biocatalytic reactions of this fungus have been reviewed recently.[2] As early as at the end of the 1960s, Fonken et al. proposed an enzyme-substrate model to account for the preferential hydroxylation by that microorganism of certain positions in cyclic alcohols or alicyclic carboxamides.[3] For the latter substrates, the model suggests that in a first step an electron-rich center, such as the carbonyl oxygen, becomes attached to the enzyme's active site. Hydroxylation then occurs selectively at a carbon atom approximately 5.5 Å distant from this oxygen atom. Succeeding investigations established an optimum distance of 4.5 to 6.2 Å for regioselective hydroxylation,[4] and this rule became the first predictive tool for the selectivity of hydroxylation of non-activated hydrocarbon positions by *B. bassiana.* Different hydroxylation models have been reviewed by Holland,[5] and a new concept of docking/protecting groups in biohydroxylation was recently published by Griengl et al.[6]

This microorganism was used by Furstoss et al. for biohydroxylation of various other substrates, and the original model was extended.[7] Mostly alicyclic amides,[8] lactams,[8b,9] and carbamates[10] have been transformed. For these substrates the authors found that the distance between the carbonyl oxygen and the hydroxylated carbon atom varied from 3.3 to 6.2 Å, so the previously described distance criterion was no longer useful as a general predictive tool.[11] Later on, other authors added more examples of hydroxylation of the above classes of compounds.[12] Even saturated carbocycles, including steroids or terpenes, a tetrahydrofuran derivative, and alkyl side chains of aromatic compounds not possessing any electron-rich functional binding group may be hydroxylated.[7,13] Moreover, the ability of this fungus to *p*-hydroxylate aromatic rings of *N*-benzoylamines, *N*-phenylcarbamates, or substituted heteroaromatics is also well known.[8,10,14] In addition, olefins are epoxidized,[3a,15] sulfoxides are produced from thioethers,[16] and even a Baeyer−Villiger oxidation of a ketone has been facilitated by this microorganism.[17] Holland et al. suggested[2] that no fewer than four distinct types of hydroxylases are responsible for the hydroxylation activity of *B. bassiana*: one monooxygenase for the hydroxylation of hydrocarbon positions in amides and related polar substrates, one for the hydroxylation of non-activated hydrocarbons lacking any directing influence from existing substrate functionality, another for the hydroxylation of benzylic positions, and the fourth for the *p*-hydroxylation of aromatic positions.

In 1997 we modified the original distance models of Fonken et al.[3] and Furstoss et al.[7] for hydroxylation, with *B. bassiana*, of non-activated hydrocarbon positions in *N*-phenylcarbamates of rigid and flexible mono- and bicyclic alcohols,[12d] taking regio- and stereoselectivity into account. After an induced fit of the substrate into the enzyme's active site, a hydrogen of a chemically non-activated methylene or methine group is replaced by an OH group by a radical "oxygen rebound" mechanism[1c,18] or a carbocationic[19] mechanism at an optimum distance of about 5.5 Å from the oxygen atom directly attached to the alicyclic

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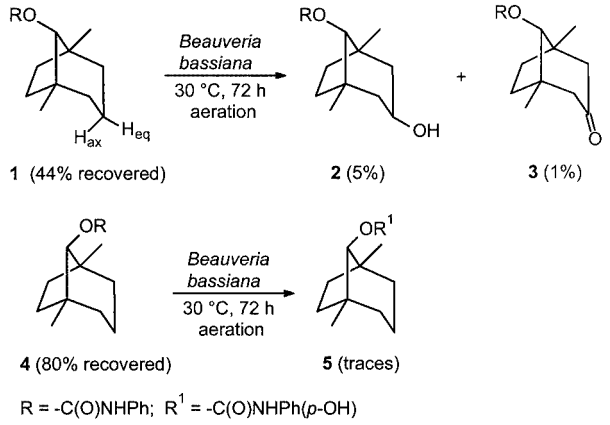


Scheme 1

part of the substrate.[12d] This is illustrated in Scheme 1 for the *N*-phenylcarbamates of two diastereomeric bicyclo-[3.2.1]octan-7-ols **1** and **4**.

In the *anti* isomer **1**, the equatorial hydrogen in position 3, at a distance of 5.2 Å (AM1 calculation) from the oxygen, is selectively replaced by a hydroxy group. This produces the alcohol **2**, which is partially dehydrogenated to afford the ketone **3**. In contrast, the *syn* isomer **4**, lacking any oxygen−hydrogen distance close to 5 Å in an alicyclic position (4.3 Å for 3-H_{ax} and 4.5 Å for 3-H_{eq}), was not hydroxylated in this part of the molecule at all, although traces of the phenol **5** were found as the sole oxygenated product (Scheme 1). Most of this substrate was recovered.[12d] In agreement with this model, cyclopentyl *N*-phenylcarbamate was also not hydroxylated at all,[10c] while all substrates containing such a distance of about 5 Å were hydroxylated in the corresponding positions.[10,12c,12d,20]

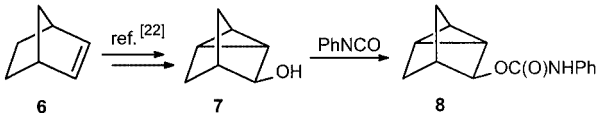
This model takes into account that the binding mode of the substrate to the enzyme's active site is dictated mainly by intrinsic steric and electronic properties of the involved electron-rich docking group.[7,11,21] Similarly, the regio- and stereochemistry of hydroxylation is determined mainly by the structure of the hydrocarbon: namely by a specific distance from the anchoring group to potentially replacable hydrogens. For the definition of the distance of potentially substituted hydrogen atoms to the oxygen atom attached directly at the alicyclic ring, distance variations caused by the mobility of the phenylcarbamate function are excluded. This oxygen can move only together with the ring carbons. Movement of the docking group indeed influences the induced fit of the substrate, but does not influence the distance of the catalytically active center that activates molecular oxygen, and the potential hydroxylation position. This distance is therefore independent of the specific conformational requirements for the induced fit of the docking group, and is also independent of the distance between the binding site and the catalytic center of the enzyme.

Recently, we have shown that the presence of a fluorine substituent in the *trans*-2-position of a carbamoyl group did not change the regioselectivity but rather influences the stereochemistry of biohydroxylation, depending on the absolute configuration of the substrate and the ring size.[12,20] Continuing our ongoing research on the regio- and stereoselectivity of microbiological hydroxylation and the influence of a single fluorine substituent in strategic positions on the selectivity of such reactions, here we present the results of synthesis and biohydroxylation of 3-nortricyclanyl *N*-phenylcarbamate (**8**) and the stereoisomeric monofluorinated analogues **13** and **14**, each bearing a fluorine atom in either the *exo*-5- or the *endo*-5-position.

Results and Discussion

Synthesis of the Carbamates

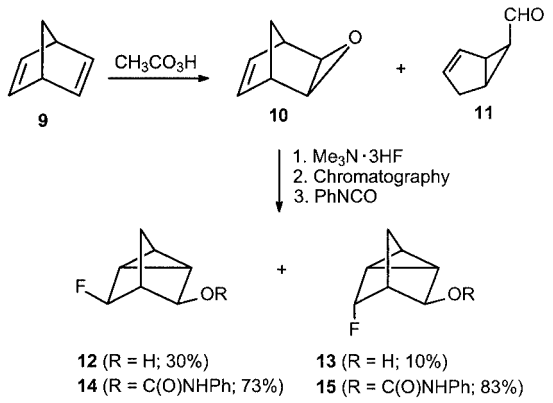
Tricyclo[2.2.1.$0^{2,6}$]heptan-3-ol (**7**) was synthesized from norbornene (**6**) by a known sequence,[22] and subsequently heated at reflux with phenyl isocyanate in petroleum ether (110−140 °C) to give the corresponding carbamate **8** in 85% yield (Scheme 2).



Scheme 2

The 5-fluoro derivatives of **8** should be available through epoxide ring-opening of *exo*-2,3-epoxynorbornene (**10**) with an acidic fluorinating agent through transannular π-participation of the double bond in an intermediary carbocation, similarly to the mechanism of bromofluorination of norbornadiene (**9**).[23] However, synthesis of the desired epoxide in pure form was difficult, because of rearrangement of **10** to *endo*-bicyclo[3.1.0]hex-2-ene-6-carbaldehyde (**11**).[24]

Thus, a CH_2Cl_2 solution containing 63−68% of **10** was prepared from **9** by treatment with buffered peracetic acid at −15 °C according to a method reported by Meinwald et al.[25] The solvent was evaporated, and the mixture was dropped into neat trimethylamine−trihydrofluoride ($Me_3N{\cdot}3HF$)[26] at 45 °C over 45 min and stirred for another 5 min. After workup, the fluorohydrins **12** (30%) and **13** (10%) were separated from the aldehyde **11** and from one another by column chromatography. The diastereomeric fluorohydrins were then heated at reflux with phenyl isocyanate in petroleum ether (80−120 °C) for 4 h to give the corresponding carbamates **14** and **15** in 73% or 83% isolated yield (Scheme 3).



Scheme 3

The assignment of the structures of the fluorohydrins **12** and **13** is demonstrated by some indicative signals. The ^{19}F NMR spectrum of the *exo*,*exo* compound **12** shows a signal at −192.0 ppm with a geminal H,F coupling constant of 59.1 Hz. This coupling constant is also found in the multiplet at δ = 4.57 ppm for 5-H in the ^{1}H NMR spectrum. The doublet of C-5 is found at δ = 93.6 ppm with $^{1}J_{C,F}$ = 190.7 Hz in the proton-decoupled ^{13}C NMR spectrum. For C-3, a doublet is found at δ = 71.2 ppm ($^{3}J_{C,F}$ = 5.1 Hz). The fluorine signal of the *exo*,*endo* compound **13** is located at −197.6 ppm. ($^{2}J_{F,H}$ = 61.0 Hz). This coupling constant is also found in the signal of 5-H at δ = 4.77 ppm in the proton NMR spectrum. The doublet corresponding to C-5 is found at δ = 98.6 ppm ($^{2}J_{C,F}$ = 188.2 Hz), while the signal for C-3 is found at δ = 74.9 ppm, not showing any coupling to the fluorine atom because of the gauche arrangement (cf. discussion in ref.[23]).

Similar signals were also found in the corresponding NMR spectra of compounds **14** and **15**. Moreover, the assignment of configuration was confirmed by X-ray analysis[27] of a single crystal of 5-*exo*-fluorotricyclo-[2.2.1.0^{2,6}]hept-3-*exo*-yl *N*-phenylcarbamate (**14**, Figure 1).

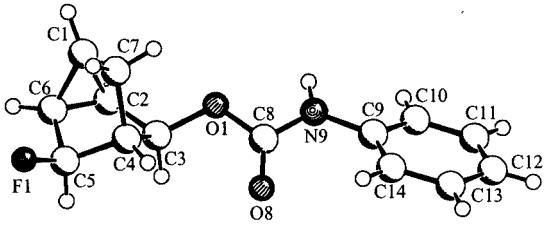
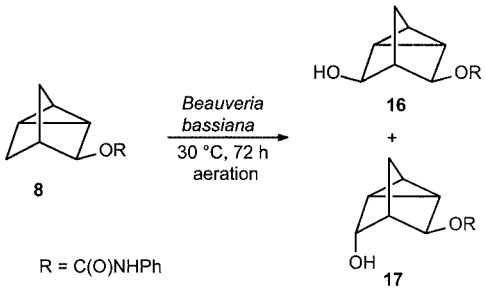


Figure 1. Crystal structure of compound **14**

Biotransformation by use of *Beauveria bassiana*

All biotransformations of compounds **8**, **14**, and **15** were performed by a standard procedure through the use of a 2 L fermenter with 200 mg substrate per liter of a growing culture of *B. bassiana* ATCC 7159.[20] In a standard medium,[12d] the culture with the substrate was aerated with 1.5 L air per minute at 30 °C for 72 h.

The biotransformation of compound **8** by this procedure gave a 7:1 mixture of the diastereomers **16** and **17** in 19% isolated yield (Scheme 4), no other hydroxylated products being found, and with 22% of the starting material being recovered. Separation of **16** from **17** was not successful. The structures of compounds **16** and **17** were assigned from spectroscopic data extracted from the spectra of the product mixture. The data for **16** agree with those observed for the major product of biotransformation of compound **8** with *Rhizopus arrhizus*.[28]



Scheme 4

Thus, the *exo* hydroxylation is strongly preferred over the *endo* hydroxylation. This might be an indication of a preferred abstraction of the 5-H_{exo}, which lies at a distance of 4.6 Å from the oxygen attached directly to the tricyclic hydrocarbon skeleton (AM1 calculation), rather than the 5-H_{endo} (distance 4.1 Å), provided that the hydroxylation occurs with retention of configuration. Surprisingly, no ring-opening of the cyclopropane ring was observed, so no hint of the nature of the intermediary species[18,19] could be obtained from the structures of the products.

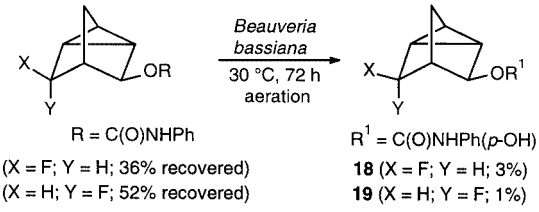
Furthermore, the optical rotation of the 7:1 mixture of **16** and **17** was determined to be $[\alpha]_D^{20}$ = +2.1. Provided that the specific rotation of the *endo* compound **17** is not significantly larger than the rotation of **16**, the enantiospecificity of *B. bassiana* is thus the opposite of that of *Rhizopus arrhizus*. The specific rotation (same solvent) of the isolated pure *exo*,*exo*-**16** in that case was determined to be $[\alpha]_D^{20}$ = −1.1.[28] The absolute configurations of the products were not assigned.

We were also interested in the influence of a fluorine substituent attached to the carbon atom to be hydroxylated. Fluorine is known to change the electronic properties of compounds dramatically without strong alterations to the steric demand.[29] The formation of additional hydrogen bonds to the enzyme might be responsible for different selectivities occasionally observed for fluorinated substrates relative to their non-fluorinated parent compounds.[30] Such observations have been applied to change the position of hydroxylation in steroids, for instance. Thus, substitution of the 6α-position in 21-hydroxy-16α-methyl-4-pregnene-3,20-dione by fluorine blocks the unwanted 7β-hydroxylation by *Curvularia lunata*, redirecting hydroxylation to the 11α- or the 9α-position.[31] Several more monofluoro- and gem-difluoro-5a-androstanones and the parent ketones have been transformed with different fungi such as *Aspergillus ochra-*

ceus. With few exceptions, hydroxylation is diverted to an alternative position neither at nor adjacent to the carbon atom to which a fluorine atom is attached, even though one of these centers in the parent compound is a favored site. Fluorine acts merely as a blocking group.[31,32] Where the favored site is more remote from the fluorine substituent(s), the behavior of a fluoro compound resembles that of its parent.[32] Holland et al. observed different enantioselectivity for the monohydroxylation of *o*-, *m*-, or *p*-fluorinated ethylbenzenes by *Mortierella isabellina*.[33]

Substitution of the natural hydroxylation position at C-5 by a geminal difluoro moiety resulted in hydroxylation of one of the geminal methyl groups of 5,5-difluorocamphor by *Pseudomonas putida* cytochrome P450.[34] On the other hand, a single fluorine substituent in the *trans*-2-position close to the anchoring group of cycloalkyl *N*-phenylcarbamates did not change the regioselectivity, but rather influenced the diastereoselectivity of hydroxylation with *B. bassiana*, depending on the absolute configuration of the substrate and ring size.[12c,12d,20]

Biotransformation of the fluorinated derivatives **14** and **15** under standard conditions resulted in very low levels of conversion of the substrates (Scheme 5).



Scheme 5

No products of hydroxylation of any alicyclic position were found. In both cases only *p*-hydroxylation of the substrates was observed, giving compound **18** in 3% yield or compound **19** in 1% isolated yield. The structures of the products were determined by NMR spectroscopy and mass spectrometry; the following signals are indicative for the structures. The proton spectrum of **18** shows the doublet for 3-H at δ = 4.66 ppm ($^4J_{H,H}$ = 1.4 Hz) and a doublet of triplets for 5-H at δ = 4.69 ppm ($^2J_{H,F}$ = 58, $^4J_{H,H}$ = 1.9 Hz). The corresponding signal for 3-H of **19** is shifted significantly downfield to δ = 5.31 ppm ($^4J_{H,H}$ = 1.7 Hz) because of the through-space effect of the fluorine atom in the *endo* position at C-5. The doublet of triplets for 5-H is located at δ = 4.80 ppm ($^2J_{H,F}$ = 59, $^4J_{H,H}$ = 2.2 Hz). The *meta*- and *ortho*-protons of the aromatic ring are found at δ = 6.75 ppm and 7.17 ppm for **18,** or at δ = 6.67 ppm and 7.21 ppm for **19**. In the ^{13}C NMR spectra of **18** and **19**, the signals for C-3 are found at δ = 74.4 ppm or 78.4 ppm and the signals for C-5 at δ = 93.1 ppm ($^1J_{C,F}$ = 193 Hz) or 97.7 ppm ($^1J_{C,F}$ = 189 Hz), respectively. In relation to the starting materials **14** and **15**, the *p*-carbons of the aromatic rings of **18** and **19** are shifted downfield from δ = 123.5 ppm to δ = 152.2 ppm or from δ = 123.4 ppm to δ = 152.0 ppm, respectively. The *p*-hydroxylation of the products is also evident from the mass spectra. Molecular ion peaks at *m*/*z* = 263 are found for both compounds. Most indicatively, a fragment peak at *m*/*z* = 135 is found, representing the cation of 4-hydroxyphenyl isocyanate. For the starting materials, corresponding phenyl isocyanate ions are identified at *m*/*z* = 119.

Conclusion

The presence of the fluorine atom at C-5, either in the *endo*- or in the *exo*-position, thus prevents hydroxylation in any position of the nortricyclane skeleton, the only oxygenation observed in biotransformation of compounds **14** and **15** being *p*-hydroxylation of the aromatic ring. In contrast, the non-fluorinated parent *N*-phenylcarbamate of nortricyclanol **8** was preferentially hydroxylated in the 5-*exo* position under identical conditions, though the calculated distance of 4.6 Å between the oxygen atom attached to the skeleton and the hydrogen to be displaced is slightly shorter than the approximately 5 Å suggested by the model.[12d]

Experimental Section

General Remarks: ^{1}H NMR (300.1 MHz), ^{13}C NMR (75.5 MHz), and ^{19}F NMR spectra (282.3 MHz) were recorded 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 Finnigan/MAT data system. The product ratios of microbial transformations were determined on the crude product mixtures by ^{19}F NMR spectroscopy or by 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 (Na_D line, λ = 589 nm). Elemental analyses were carried out by the Microanalytical Laboratory, Organic Chemistry Institute, University of Münster, on a Foss Heraeus CHN-O analyzer.

Nortricyclanol (**7**) was synthesized in two steps from norbornene (**6**) by a procedure reported by Roberts et al.[22] This compound was then heated at reflux with phenyl isocyanate (10% excess) in petroleum ether (110−140 °C) for 24 h to give 85% of compound **8** after recrystallization from the same solvent. M.p. 148 °C (ref.[22] 146−147.5 °C). All spectroscopic data agree with those published recently.[28]

2,3-*exo*-Epoxynorborn-5-ene (10): Norbornadiene (**9**, 18.4 g, 0.2 mol) and NaOAc (24.0 g, 0.29 mol) in CH_2Cl_2 (100 mL) were cooled to −20 °C in a 500-mL two-necked round-bottomed flask fitted with a thermometer, a dropping funnel, and an efficient stirrer bar. Peracetic acid (40%, 44 mL, 0.23 mol) was dropped into the mixture with vigorous stirring over a period of 2 h, with the temperature being maintained below −15 °C. After complete addition of the peracid, stirring at −15 °C was continued for another 15 min. The mixture was warmed slowly to +5 °C and was then poured into ice-cold aqueous $Na_2S_2O_7$ solution (0.1 M, 150 mL). This mixture was transferred into a separation funnel and shaken, and the phases were separated. The organic layer was shaken again with another portion of the thiosulfate solution mentioned

(150 mL) and subsequently twice with a saturated aq. solution of NaOAc. The organic layer was dried with $MgSO_4$, the solvent was evaporated at about 10 °C, and the yellowish liquid (8.7 g) solidified at −18 °C. The content of epoxide **10** was gas chromatographically determined to be 63−68%. In addition, 10−15% of norbornadiene (**9**) and 15−20% of the aldehyde **11** were found. The spectroscopic data determined for **10** from the spectra of the mixture containing 68% of **10** agree with those published in ref.[24]

Epoxide Ring-Opening with Trimethylamine−Trihydrofluoride

Trimethylamine−trihydrofluoride (595 mg, 5 mmol) was placed in a 10 mL two-necked flask, fitted with a gas pipe and a septum, and heated at 45 °C. At this temperature, a sample of the mixture as prepared above, containing 63% of the epoxide **10** (422 mg, 2.5 mmol), was added dropwise by syringe, with stirring, over 45 min. Stirring was then continued for an additional 5 min. After cooling to room temperature, the mixture was dissolved in CH_2Cl_2 (10 mL). Water (15 mL) was added and the mixture was neutralized with concentrated ammonia solution. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with concentrated NaCl solution (15 mL) and dried over $MgSO_4$. Besides some quantities of norbornadiene (**9**) and the aldehyde **11**, the mixture contained a 3:1 mixture (GC) of the fluorohydrins **12** and **13**. These products were separated from one another and from the impurities by column chromatography on silica gel (15 g) by use of pentane/diethyl ether (1:1) as eluent.

3-*exo*,5-*exo*-Fluorotricyclo[2.2.1.0^{2,6}]heptan-3-ol (12): Yield: 96 mg (30%). M.p. 82−86 °C (pentane/diethyl ether). ^{1}H NMR: δ = 1.36−1.63 (m, 3 H, 1-H, 2-H, 6-H), 1.79−1.95 (m, 2 H, 7-H_2), 2.11−2.19 (br. s, 1 H, 4-H), 3.82 (q, $^4J_{H,H}$ = 1.8 Hz, 1 H, 3-H), 4.57 (dt, $^2J_{H,F}$ = 58.9, $^4J_{H,H}$ = 1.9 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 12.4 (d, C-1), 19.0 (dd, $^2J_{C,F}$ = 25.4 Hz, C-6), 21.5 (dd, $^3J_{C,F}$ = 5.1 Hz, C-2), 26.4 (t, C-7), 40.5 (dd, $^2J_{C,F}$ = 12.7 Hz, C-4), 71.2 (dd, $^3J_{C,F}$ = 5.1 Hz, C-3), 93.6 (dd, $^1J_{C,F}$ = 190.7 Hz, C-5) ppm. ^{19}F NMR: δ = −192.0 (d, $^2J_{F,H}$ = 59.1 Hz, 5-F) ppm. MS (GC/MS, ion trap): *m*/*z* (%) = 127 (5) [M^+ − 1], 109 (48), 99 (9), 91 (42), 84 (18), 79 (100), 72 (9), 66 (63), 51 (13), 43 (8), 39 (51). C_7H_9FO (128.1): calcd. C 65.61, H 7.08; found C 65.43, H 7.22.

3-*exo*,5-*endo*-Fluorotricyclo[2.2.1.0^{2,6}]heptan-3-ol (13): Yield: 32 mg (10%). M.p. 59−63 °C (pentane/diethyl ether). ^{1}H NMR: δ = 1.38−1.62 (m, 4 H, 1-H, 2-H, 6-H, 7-H_{2b}), 1.79−1.95 (dd, $^2J_{H,H}$ = 11.0, $^4J_{H,H}$ = 1.4 Hz, 1 H, 7-H_{2a}), 2.01 (br. d, 1 H, 4-H), 4.54 (q, $^4J_{H,H}$ = 1.7 Hz, 1 H, 3-H), 4.77 (dt, $^2J_{H,F}$ = 59.4, $^4J_{H,H}$ = 2.1 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 15.1 (dd, $^3J_{C,F}$ = 7.6 Hz, C-2), 17.8 (dd, $^2J_{C,F}$ = 25.4 Hz, C-6), 18.2 (d, C-1), 26.2 (t, C-7), 40.0 (dd, $^2J_{C,F}$ = 15.3 Hz, C-4), 74.9 (d, C-3), 98.6 (dd, $^1J_{C,F}$ = 188.2 Hz, C-5) ppm. ^{19}F NMR: δ = −197.6 (d, $^2J_{F,H}$ = 61.0 Hz, 5-F) ppm. MS (GC/MS, ion trap): *m*/*z* (%) = 127 (5) [M^+ − 1], 109 (83), 99 (12), 91 (85), 85 (22), 79 (100), 72 (7), 66 (92), 53 (15), 43 (4), 39 (65). C_7H_9FO (128.1): calcd. C 65.61, H 7.08; found C 65.81, H 7.10.

3-*exo*,5-*exo*-Fluorotricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-Phenylcarbamate (14): The fluorohydrin **12** (512 mg, 4 mmol) was heated at reflux with phenyl isocyanate (524 mg, 4.4 mmol) in petroleum ether (110−140 °C) for 24 h by the procedure given in ref.[12c], and the mixture was worked up to give **14**. Yield: 721 mg (73%). M.p. 116−120 °C (petroleum ether). ^{1}H NMR: δ = 1.54−1.70 (m, 3 H, 1-H, 2-H, 6-H), 1.88 (d, $^2J_{H,H}$ = 10.7 Hz, 1 H, 7-H_2), 1.97 (dd, $^2J_{H,H}$ = 10.7, $^4J_{H,H}$ = 1.0 Hz, 1 H, 7-H_2), 2.41 (br. s, 1 H, 4-H), 4.68 (d, $^4J_{H,H}$ = 1.7 Hz, 1 H, 3-H), 4.70 (dt, $^2J_{H,F}$ = 58.2, $^4J_{H,H}$ = 1.9 Hz, 1 H, 5-H), 6.72 (br. s, 1 H, NH), 7.05 (tt, $^3J_{H,H}$ = 7.2, $^4J_{H,H}$ = 1.2 Hz, 1 H, *p*-H), 7.29 (t, $^3J_{H,H}$ = 8.0 Hz, 2 H, *m*-H), 7.35 (br. d, $^3J_{H,H}$ = 11.9 Hz, 2 H, *o*-H) ppm. ^{13}C NMR: δ = 13.0 (d, C-1), 18.6 (dd, $^2J_{C,F}$ = 25.4 Hz, C-6), 19.4 (dd, $^3J_{C,F}$ = 5.1 Hz, C-2), 27.4 (t, C-7), 38.5 (dd, $^2J_{C,F}$ = 17.8 Hz, C-4), 74.3 (dd, $^3J_{C,F}$ = 5.1 Hz, C-3), 93.0 (dd, $^1J_{C,F}$ = 193.3 Hz, C-5), 118.7 (2d, *o*-C), 123.5 (d, *p*-C), 129.0 (2d, *m*-C), 137.6 (s, *ipso*-C), 152.8 (s, C=O) ppm. ^{19}F NMR: δ = −193.2 (d, $^2J_{F,H}$ = 59.1 Hz, 5-F) ppm. MS (GC/MS): *m*/*z* (%) = 248 (9) [M^+ + 1), 247 (54) [M^+], 204 (1), 203 (5), 183 (5), 182 (6), 137 (5) [$C_6H_5NHCO_2H^+$], 120 (5), 119 (25) [137 − H_2O], 111 (100) [$C_7H_8F^+$], 109 (38), 104 (7), 93 (24) [$C_6H_5NH_2^+$], 91 (45) [$C_7H_7^+$], 83 (5), 77 (14) [$C_6H_5^+$], 66 (4), 65 (11), 59 (4), 51 (6), 39 (8). $C_{14}H_{14}FNO_2$ (247.3): calcd. C 68.01, H 5.71, N 5.67; found C 67.86, H 5.74, N 5.56.

3-*exo*,5-*endo*-Fluorotricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-Phenylcarbamate (15): The carbamate **15** was synthesized from the fluorohydrin **13** as described above for compound **14**. Yield: 820 mg (83%). M.p. 127−129 °C (petroleum ether). ^{1}H NMR: δ = 1.43−1.65 (m, 3 H, −CH, −CH_2), 1.75 (tm, $^3J_{H,H}$ = 5.0 Hz, 1 H, −CH) 1.86 (dd, $^2J_{H,H}$ = 11.0, $^4J_{H,H}$ = 1.4 Hz, 1 H, 7-H_{2a}), 2.28 (br. s, 1 H, 4-H), 4.81 (dt, $^2J_{H,F}$ = 58.7, $^4J_{H,H}$ = 2.2 Hz, 1 H, 5-H), 5.33 (q, $^4J_{H,H}$ = 1.7 Hz, 1 H, 3-H), 6.59 (br. s, 1 H, NH), 7.04 (tt, $^3J_{H,H}$ = 7.3, $^4J_{H,H}$ = 1.3 Hz, 1 H, *p*-H), 7.29 (tt, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.9 Hz, 2 H, *m*-H), 7.36 (br. d, $^3J_{H,H}$ = 7.4 Hz, 2 H, *o*-H) ppm. ^{13}C NMR: δ = 15.3(dd, $^3J_{C,F}$ = 7.6 Hz, C-6), 16.0 (d, C-1), 17.3 (dd, $^2J_{C,F}$ = 22.9 Hz, C-2), 27.0 (dt, $^3J_{C,F}$ = 5.1 Hz, C-7), 38.0 (dd, $^2J_{C,F}$ = 15.3 Hz, C-4), 78.5 (d, C-3), 97.7 (dd, $^1J_{C,F}$ = 188.2 Hz, C-5), 118.7 (2d, *o*-C), 123.4 (d, *p*-C), 129.0 (2d, *m*-C), 137.8 (s, *ipso*-C), 153.1 (s, C=O) ppm. ^{19}F NMR: δ = −196.7 (d, $^2J_{F,H}$ = 59.1 Hz, 5-F) ppm. MS (GC/MS): *m*/*z* (%) = 250 (2), 248 (15) [M^+ + 1), 247 (81) [M^+], 203 (4), 182 (16), 137 (25) [$C_6H_5NHCO_2H^+$], 119 (36) [137 − H_2O], 111 (81) [$C_7H_8F^+$], 91 (100) [$C_7H_7^+$], 77 (29) [$C_6H_5^+$], 65 (11), 39 (8). $C_{14}H_{14}FNO_2$ (247.3): calcd. C 68.01, H 5.71, N 5.67; found C 68.15, H 5.78, N 5.79.

Biotransformation with *Beauveria bassiana* ATCC 7159: The *N*-phenylcarbamates **8**, **14**, or **15** (300 mg each) were transformed through the use of a growing culture of *B. bassiana* ATCC 7159 as described in ref.[12c,20]

3-*exo*,5-*exo*-Hydroxytricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-Phenylcarbamate (16) and 3-*exo*,5-*endo*-Hydroxytricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-Phenylcarbamate (17): Together with the starting material **8** (66 mg, 22%), a 7:1 mixture of compounds **16** and **17** (62 mg, 19%) was isolated. M.p. 128 °C (cyclohexane/ethyl acetate, 1:1). $[\alpha]_D^{22}$ = +2.1 (*c* = 1, $CHCl_3$). The spectroscopic data for **16** agree with those reported recently.[28] For the isomer **17** the following data were extracted from the spectra of the 7:1 mixture: ^{1}H NMR: δ = 1.35−1.99 (m, 1-H, 2-H, 5-H_2, 6-H, 7-H_2, −OH), 2.05 (s, 1 H, 4-H), 4.47 (m, 1 H, 5-H), 4.78 (m, 1 H, 3-H), 6.74 (br. s, 1 H, NH), 7.03 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, *p*-H), 7.28 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, *m*-H), 7.34 (br. d, $^3J_{H,H}$ = 7.9 Hz, 2 H, *o*-H) ppm. ^{13}C NMR: δ = 14.1(d, C-1), 17.8 (d, C-2), 20.7 (d, C-6), 27.1 (t, C-7), 39.5 (d, C-4), 75.2 (d, C-5), 80.7 (d, C-3), 118.7 (d, *o*-C), 123.2 (d, *p*-C), 128.9 (d, *m*-C), 137.9 (s, *ipso*-C), 153.4 (s, C=O) ppm. MS (GC-MS, 70 eV, ion trap): *m*/*z* (%) = 245 (4) [M^+], 207 (2), 119 (26) [$C_6H_5NCO^+$], 109 (18) [$C_7H_9O^+$] 93 (57) [$C_6H_5NH_2^+$], 79 (100) [$C_6H_7^+$], 77 (53) [$C_6H_5^+$], 65 (34), 51 (23), 39 (53) [$C_3H_3^+$].

3-*exo*,5-*exo*-Fluorotricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-(4-Hydroxyphenyl)-carbamate (18): Compound **18** (8 mg, 3%) was isolated together with starting material **14** (109 mg, 36%). ^{1}H NMR: δ = 1.55−1.68 (m, 3 H, 1-H, 2-H, 6-H), 1.81−2.00 (d, $^2J_{H,H}$ = 10.7 Hz, 1 H, 7-H_2), 1.96 (dd, $^4J_{H,H}$ = 10.7, $^4J_{H,H}$ = 1.0 Hz, 1 H, 7-H_2), 2.39 (br. s, 1 H, 4-H), 4.66 (d, $^4J_{H,H}$ = 1.4 Hz, 1 H, 3-H), 4.69 (dt, $^2J_{H,F}$ =

58.4, $^4J_{H,H}$ = 1.9 Hz, 1 H, 5-H), 6.41 (br. s, 1 H, NH), 6.75 (dt, $^3J_{H,H}$ = 10.0, $^4J_{H,H}$ = 2.9 Hz, 2 H, *m*-H), 7.17 (br. d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *o*-H) ppm. ^{13}C NMR: δ = 13.1 (d, C-1), 18.7 (dd, $^2J_{C,F}$ = 24.6 Hz, C-6), 19.5 (d, C-2), 27.5 (t, C-7), 38.6 (dd, $^2J_{C,F}$ = 16.0 Hz, C-4), 74.4 (d, C-3), 93.1 (dd, $^1J_{C,F}$ = 193.4 Hz, C-5), 115.8 (2d, *o*-C), 121.5 (2d, *m*-C), 130.5 (s, *ipso*-C), 152.2 (s, *p*-C), 153.4 (s, C=O) ppm. ^{19}F NMR: δ = −193.3 (d, $^2J_{F,H}$ = 57.2 Hz, 5-F) ppm. MS (GC/MS): *m*/*z* (%) = 263 (36) [M^+], 219 (11), 198 (8), 172 (7), 153 (9), 135 (31) [$C_6H_4NHCO_2^+$], 120 (10), 111 (90) [$C_7H_8F^+$], 91 (100) [$C_6H_4NH^+$], 81 (11) [$C_6H_9^+$], 65 (16) [$C_5H_5^+$], 39 (15) [$C_3H_3^+$].

3-*exo*,5-*endo*-Fluorotricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-(4-Hydroxyphenyl)carbamate (19): Compound **19** (3 mg, 1%) was isolated together with starting material **15** (157 mg, 52%). ^{1}H NMR: δ = 1.43−1.67 (m, 3 H, −CH, $-CH_2$), 1.73 (tm, $^3J_{H,H}$ = 4.4 Hz, 1 H, −CH) 1.86 (d, $^2J_{H,H}$ = 10.0 Hz, 1 H, 7-H_{2a}), 2.27 (br. s, 1 H, 4-H), 4.80 (dt, $^2J_{H,F}$ = 58.7, $^4J_{H,H}$ = 2.2 Hz, 1 H, 5-H), 5.31 (d, $^4J_{H,H}$ = 1.7 Hz, 1 H, 3-H), 6.39 (br. s, 1 H, NH), 6.76 (dt, $^3J_{H,H}$ = 8.8, $^4J_{H,H}$ = 2.8 Hz, 2 H, *m*-H), 7.21 (br. d, $^3J_{H,H}$ = 8.6 Hz, 2 H, *o*-H) ppm. ^{13}C NMR: δ = 15.4 (d, C-1), 16.0 (d, C-2), 17.3 (dd, $^2J_{C,F}$ = 23.1 Hz, C-6), 27.1 (t, C-7), 38.1 (dd, $^2J_{C,F}$ = 15.9 Hz, C-4), 78.4 (d, C-3), 97.7 (dd, $^1J_{C,F}$ = 188.8 Hz, C-5), 115.8 (2d, *o*-C), 121.0 (2d, *m*-C), 129.1 (s, *ipso*-C) 152.0 (s, *p*-C), 153.5 (s, C=O) ppm. ^{19}F NMR: δ = −196.7 (d, $^2J_{F,H}$ = 61.0 Hz, 5-HF) ppm. MS (GC/MS): *m*/*z* (%) = 263 (22) [M^+], 243 (2) [M^+ − HF], 219 (5), 198 (4), 172 (7), 153 (13), 135 (18) [$C_6H_4NHCO_2^+$], 111 (40) [$C_7H_8F^+$], 91 (100) [111 − HF], 79 (21) [$C_6H_7^+$], 65 (13) [$C_5H_5^+$], 52 (15), 39 (11) [$C_3H_3^+$].

X-ray Crystallographic Study

3-*exo*,5-*exo*-Fluorotricyclo[2.2.1.0^{2,6}]hept-3-yl *N*-Phenylcarbamate (14): Formula $C_{14}H_{14}FNO_2$, M = 247.26, colorless crystal 0.25 × 0.15 × 0.10 mm, a = 10.974(3), b = 9.812(4), c = 22.542(12) Å, V = 2427.3(18) Å^3, $\rho_{calcd.}$ = 1.353 g cm^{-3}, μ = 8.39 cm^{-1}, empirical absorption correction via ψ scan data (0.818 ≤ T ≤ 0.921), Z = 8, orthorhombic, space group *Pbca* (No. 61), λ = 1.54178 Å, T = 223 K, ω scans, 2069 reflections collected (+h, −k, +l), [(sinθ)/λ] = 0.59 Å^{-1}, 2069 independent and 912 observed reflections [$I \geq 2\sigma(I)$], 194 refined parameters, R = 0.078, wR^2 = 0.182, maximal residual electron density 0.30 (−0.28) e·Å^{-3}, hydrogen at N9 from difference Fourier calculation, others calculated and all refined as riding atoms, poorly diffracting crystal, positional disorder of the group C1 to C7 including F1 refined with split positions to a ratio of 0.64(1):0.36, due to the small amount of observed data the minor component was refined with isotropic thermal parameters.

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[1] [1a] G. S. Fonken, R. A. Johnson, *Chemical Oxidations with Microorganisms*, Marcel Dekker, New York, **1972**, p. 1−83. [1b] H. L. Holland, *Organic Synthesis with Oxidative Enzymes*, VCH Publishers, New York, **1992**. [1c] P. R. Ortiz de Montellano, *Cytochrome P-450, Mechanism and Biochemistry*, 2nd ed., Plenum Press, New York, **1995**. [1d] *Enzyme Catalysis in Organic Synthesis* (Eds.: K. Drauz, H. Waldmann), VCH Verlagsgesellschaft, Weinheim, **1995**, p. 667−807. [1e] H. L. Holland, in *Biotechnology*, 2nd ed. (Eds.: H.-J. Rehm, G. Reed), vol. 8a (Ed.: D. R. Kelly), Wiley-VCH, Weinheim, **1998**, p. 475−553. [1f] K. Faber, *Biotransformations in Organic Chemistry*, 4th ed., Springer, Berlin, **2000**, p. 225−236.

[2] [2a] H. L. Holland, T. A. Morris, P. J. Nava, M. Zabic, *Tetrahedron* **1999**, *55*, 7441−7460. [2b] G. J. Grogan, H. L. Holland, *J. Mol. Catal. B, Enzym.* **2000**, *9*, 1−32.

[3] [3a] G. S. Fonken, M. E. Herr, H. C. Murray, L. M. Reineke, *J. Am. Chem. Soc.* **1967**, *89*, 672−675. [3b] R. A. Johnson, M. E. Herr, H. C. Murray, G. S. Fonken, *J. Org. Chem.* **1968**, *33*, 3217−3221.

[4] [4a] R. A. Johnson, M. E. Herr, H. C. Murray, G. S. Fonken, *J. Org. Chem.* **1970**, *35*, 622−626. [4b] M. E. Herr, H. C. Murray, G. S. Fonken, *J. Med. Chem.* **1971**, *14*, 842−845.

[5] H. L. Holland, *Catalysis Today* **1994**, *22*, 427−440.

[6] [6a] G. Braunegg, A. de Raadt, S. Feichenhofer, H. Griengl, I. Kopper, A. Lehmann, H. Weber, *Angew. Chem.* **1999**, *111*, 2946−2949; *Angew. Chem. Int. Ed.* **1999**, *38*, 2763−2766. [6b] A. de Raadt, B. Fetz, H. Griengl, M. F. Klingler, I. Kopper, B. Krenn, D. F. Münzer, R. G. Ott, P. Plachota, H. J. Weber, G. Braunegg, W. Mosler, R. Saf, *Eur. J. Org. Chem.* **2000**, 3835−3847. [6c] A. de Raadt, H. Griengl, H. Weber, *Chem. Eur. J.* **2001**, *7*, 27−31. [6d] A. de Raadt, B. Fetz, H. Griengl, M. F. Klingler, B. Krenn, K. Mereiter, D. F. Münzer, P. Plachota, H. J. Weber, R. Saf, *Tetrahedron* **2001**, *57*, 8151−8157.

[7] [7a] A. Archelas, R. Furstoss, B. Waegell, J. Le Petit, L. Deveza, *Tetrahedron* **1984**, *40*, 355−367. [7b] R. Furstoss, A. Archelas, J.-D. Fourneron, B. Vigne, in *Organic Synthesis an Interdisciplinary Challenge* (Eds.: J. Streith, H. Prinzbach, G. Schill), Blackwell, Oxford **1985**, p. 215−226.

[8] [8a] J.-D. Fourneron, A. Archelas, B. Vigne, R. Furstoss, *Tetrahedron* **1987**, *43*, 2273−2284. [8b] A. Archelas, J.-D. Fourneron, R. Furstoss, *J. Org. Chem.* **1988**, *53*, 1797−1799. [8c] J.-D. Fourneron, A. Archelas, R. Furstoss, *J. Org. Chem.* **1989**, *54*, 2478−2483.

[9] A. Archelas, R. Furstoss, B. Vigne, G. Manry, *Bull. Soc. Chim. Fr.* **1986**, 234−238.

[10] [10a] B. Vigne, A. Archelas, J.-D. Fourneron, R. Furstoss, *Tetrahedron* **1986**, *42*, 2451−2456. [10b] B. Vigne, A. Archelas, J.-D. Fourneron, R. Furstoss, *Nouv. J. Chim.* **1987**, *11*, 297−298. [10c] B. Vigne, A. Archelas, R. Furstoss, *Tetrahedron* **1991**, *47*, 1447−1458, and references cited therein. [10d] S. J. Aitken, G. Grogan, C. S. Y. Chow, N. J. Turner, S. L. Flitsch, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3365−3370.

[11] R. Furstoss, A. Archelas, J.-D. Fourneron, B. Vigne, in *Enzymes as Catalysts in Organic Synthesis* (Ed.: M. P. Schneider), NATO ASI Series, vol. 186, **1986**, p. 361−370.

[12] [12a] R. A. Johnson, M. E. Herr, H. C. Murray, C. G. Chidester, F. Han, *J. Org. Chem.* **1992**, *57*, 7209−7212. [12b] R. A. Johnson, M. E. Herr, H. C. Murray, W. C. Krueger, L. M. Pschigoda, D. J. Duchamp, *J. Org. Chem.* **1992**, *54*, 7212−7216. [12c] S. Pietz, R. Fröhlich, G. Haufe, *Tetrahedron* **1997**, *53*, 17055−17066. [12d] S. Pietz, D. Wölker, G. Haufe, *Tetrahedron* **1997**, *53*, 17067−17078. [12e] C. R. Davis, R. A. Johnson, J. I. Chialdella, W. F. Liggett, S. A. Mizsak, V. P. Marshall, *J. Org. Chem.* **1997**, *62*, 2244−2251.

[13] [13a] G. O. Buchanan, L. A. D. Williams, P. B. Reese, *Phytochemsitry* **2000**, *54*, 39−45. [13b] G. O. Buchanan, P. B. Reese, *Phytochemsitry* **2001**, *56*, 141−151. [13c] G. Grogan, J. T. Sime, N. J. Turner, *Biotechnology Lett.* **2001**, *23*, 119−124.

[14] [14a] D. A. Griffith, D. E. Brown, S. G. Jezequel, *Xenobiotica* **1993**, *23*, 1085−1100. [14b] V. Gotor, M. Quirós, R. Liz, J. Frigola, R. Fernández, *Tetrahedron* **1997**, *53*, 6421−6432. [14c] M. Kittelmann, L. Oberer, W. Blum, O. Ghisalba, *Chimia* **1999**, *53*, 594−596.

[15] C. F. Palmer, B. Webb, S. Broad, S. Casson, R. McCague, A. J. Willetts, S. M. Roberts, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1299−1302.

[16] [16a] H. L. Holland, F. M. Brown, *Tetrahedron: Asymmetry* **1998**, *9*, 535−538. [16b] H. L. Holland, P. R. Andreana, F. M. Brown, *Tetrahedron: Asymmetry* **1999**, *10*, 2833−2843.

[17] F. Donzelli, C. Fuganti, M. Mendozza, G. Pedrocchi-Fantoni,

S. Servi, G. Zucchi, *Tetrahedron: Asymmetry* **1996**, *7*, 3129−3134.
[18] [18a] J. T. Groves, G. A. McClusky, *J. Am. Chem. Soc.* **1976**, *98*, 859−861. [18b] J. T. Groves, Y.-Z. Han, in ref.[1c], p. 3−48. [18c] W.-D. Woggon, *Top. Curr. Chem.* **1996**, *184*, 39−96. [18d] N. Harris, S. Cohen, M. Filatov, F. Ogliaro, S. Shaik, *Angew. Chem.* **2000**, *112*, 2070−2074; *Angew. Chem. Int. Ed.* **2000**, *39*, 2003−2007.
[19] [19a] M. Newcomb, F.-H. Le Tadic-Biadatti, D. L. Chestney, E. S. Roberts, P. F. Hollenberg, *J. Am. Chem. Soc.* **1995**, *117*, 12085−12091. [19b] M. Newcomb, R. Shen, S.-Y. Choi, P. H. Toy, P. F. Hollenberg, A. D. N. Vaz, M. J. Coon, *J. Am. Chem. Soc.* **2000**, *122*, 2677−2686, and references cited therein.
[20] G. Haufe, D. Wölker, R. Fröhlich, *J. Org. Chem.* **2002**, *67*, 3022−3027.
[21] W. Carruthers, J. D. Prail, S. M. Roberts, A. J. Willetts, *J. Chem. Soc., Perkin Trans. 1* **1990**, 2854−2856.
[22] J. D. Roberts, E. R. Trumbull, W. Bennett, R. Armstrong, *J. Am. Chem. Soc.* **1950**, *72*, 3116−3124.
[23] G. Alvernhe, D. Anker, A. Laurent, G. Haufe, C. Beguin, *Tetrahedron* **1988**, *44*, 3551−3563.
[24] [24a] R. W. Murray, M. K. Pillay, R. Jeyaraman, *J. Org. Chem.* **1988**, *53*, 3007−3011. [24b] L. I. Kasyan, *Russ. Chem. Rev.* **1998**, *67*, 263−278.
[25] J. Meinwald, S. S. Labana, L. L. Labana, G. H. Wahl, Jr., *Tetrahedron Lett.* **1965**, 1789−1793.
[26] Trimethylamine−trihydrofluoride ($Me_3N{\cdot}3HF$) has been shown to react slightly more selectively than the usually applied triethylamine−trihydrofluoride ($Et_3N{\cdot}3HF$). [26a] A. Sattler, G. Haufe, *J. Fluorine Chem.* **1994**, *69*, 185−190. [26b] G. Haufe, *J. Prakt. Chem.* **1996**, *338*, 99−113. [26c] D. Wölker, G. Haufe, *J. Org. Chem.* **2002**, *67*, 3015−3021.
[27] CCDC-197806 contains the supplementary crystallographic data (excluding structure factors) for compound **14**. 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; Email: deposit@ccdc.cam.ac.uk].
[28] W.-R. Abraham, H.-A. Arfmann, K. Kieslich, G. Haufe, *Biocatalysis and Biotransformation* **2000**, *18*, 283−290.
[29] [29a] J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, John Wiley & Sons, New York, **1991**. [29b] *Organofluorine Chemistry: Principles and Commercial Applications* (Eds.: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum Press, New York, **1994**. [29c] *Biomedical Frontiers of Fluorine Chemistry* (Eds.: J. Ojima, J. R. McCarthy, J. T. Welch), ACS Symposium Series 639, American Chemical Society, Washington, **1996**. [29d] D. O'Hagan, H. S. Rzepa, *Chem. Commun.* **1997**, 645−652. [29e] M. Schlosser, *Angew. Chem.* **1998**, *110*, 1538−1556; *Angew. Chem. Int. Ed.* **1998**, *37*, 1496−1513. [29f] B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3−11.
[30] [30a] A. W. Baker, A. T. Shulgin, *Nature (London)* **1965**, *206*, 712−713. [30b] H. Plenio, *Chem. Rev.* **1997**, *97*, 3363−3384. [30c] J. L. Alderfer, A. V. Eliseev, *J. Org. Chem.* **1997**, *62*, 8225−8226. [30d] J. Huang, K. Hedberg, *J. Am. Chem. Soc.* **1989**, *111*, 6909−6913.
[31] K. Kieslich, K. Petzold, H. Kosmol, W. Koch, *Liebigs Ann. Chem.* **1969**, *726*, 168−176.
[32] T. G. C. Bird, P. M. Fredericks, E. R. H. Jones, G. D. Meakins, *J. Chem. Soc., Perkin Trans. 1* **1980**, 750−755.
[33] [33a] H. L. Holland, E. J. Bergen, P. C. Chenchaiah, S. H. Khan, B. Munoz, R. W. Nimiss, D. Richards, *Can. J. Chem.* **1987**, *65*, 502−507. [33b] H. L. Holland, L. J. Allen, M. J. Chernishenko, M. Diez, A. Kohl, J. Ozog, J.-X. Gu, *J. Mol. Cat. B: Enzymatic* **1997**, *3*, 311−324.
[34] [34a] K. S. Eble, D. H. Dawson, *J. Biol. Chem.* **1984**, *259*, 14389−14393. [34b] S. Kadkhodayan, E. D. Coulter, D. M. Maryniak, T. A. Bryson, J. H. Dawson, *J. Biol. Chem.* **1995**, *270*, 28042−28048.

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