DOI: 10.1002/ejoc.201001224

Synthesis and Preferred Conformations of All Regio- and Diastereoisomeric Methyl 2,3-Fluorohydroxyalkanoates

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Keywords: Organofluorine chemistry / Fluorohydrins / Conformation analysis / Enantioselectivity / Nucleophilic substitution / Quantum chemical calculations

Selective syntheses of enantiopure regio- and diastereomeric methyl 2,3-fluoro-hydroxyalkanoates via four different routes employing two types of fluorination reagents are reported. The *anti*- and *syn*-3-fluoro-2-hydroxyalkanoates **1** and **3** were prepared by treating the corresponding epoxides with Olah's reagent (Py·9HF). Cyclic sulfates prepared from the enantiomeric diols were ring-opened with TBAF to give the *anti*- and *syn*-2-fluoro-3-hydroxyalkanoates **2** and **4**. The stereochemical analysis was performed mainly by NMR spectroscopy. Applying DFT/B3LYP and SCS-MP2 quantum chemical methods, the coupling constants and relative energies of conformers were calculated. Solvent effects were considered using the COSMO continuum model.

Introduction

The substitution of a C–H group by a C–F group causes dramatic changes of the physico-chemical properties, of the chemical reactivity, and of the biological behavior of molecules.[1] On the one hand a fluorine substituent is almost isosteric to hydrogen and isopolar to the OH group. This results in the ability of a C–F group to act as a weak hydrogen-bond acceptor with respect to polar X–H-bonds, though this point is still discussed.[2] Due to the similarity of the bond lengths of aliphatic C–F and C–O bonds (1.39 and 1.43 Å, respectively) and their comparable polarity, the fluorine substituent can act as a mimic for a hydroxy group. Although hydrogen bonds of fluorine to OH groups are weaker than those of the other halogens, they lead to the preference of a *gauche* conformation of fluoroethanol in the liquid.[3,4] Similar observations both by NMR spectroscopy and quantum chemical calculations were also made for the vicinal fluorohydrin fragment in 1,3-difluoropropan-2-ol and 1-(4-bromophenyl)-2-fluoroethanol as well as for 2-fluoropropanol and *trans*-2-fluorocyclohexanol.[5] Conformations of fluorohydrins derived from long-chain α,β-unsaturated fatty acid esters, where the ester function will significantly influence the geometry, are not yet known.

In order to study the phase behavior at interfaces of such long-chain fluorinated fatty acid esters,[6] we were interested in regio- and stereoselective synthesis of diastereomeric 2,3-fluorohydrins derived from α,β-unsaturated fatty acid esters and to determine the lowest energy conformations by NMR methods and high level quantum chemical calculations for shorter-chain model compounds. Since the phase behavior depends on the enantiomeric excess, it was necessary to prepare highly enantiopure material.[7]

For the synthesis of vicinal fluorohydrins *anti*-selective epoxide ring opening with fluorinating reagents is one of the most frequently used methods, which allows the introduction of a fluorine atom into a broad variety of carbon skeletons. Various reagents or reagent combinations have been used as fluoride donors.[8] Ring opening can occur by different reaction mechanisms, S_N1 or S_N2, explaining the selectivity of the formal addition of HF. Carbenium ion-stabilizing substituents favor an S_N1 reaction, whereas destabilizing substituents favor the S_N2 pathway. Additionally, the selectivity of these reactions is influenced by steric constraints, the acidity of the reagent, the nucleophilicity of the particular fluoride donor, the solvent and the reaction temperature.[9]

Results and Discussion

Synthesis of Regio- and Stereoisomeric Methyl 2,3-Fluorohydroxyalkanoates

For the selective synthesis of the regioisomeric methyl 2,3-fluorohydroxyalkanoates four different routes were used. The racemic methyl *anti*-3-fluoro-2-hydroxyalkanoates **1** were obtained by ring opening with hydrofluorinating agents of the racemic epoxides **6**, which were available from the α,β-unsaturated esters **5** by epoxidation using

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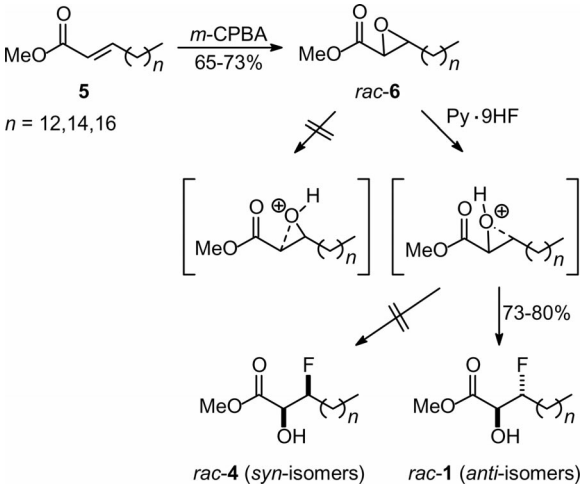
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001224.

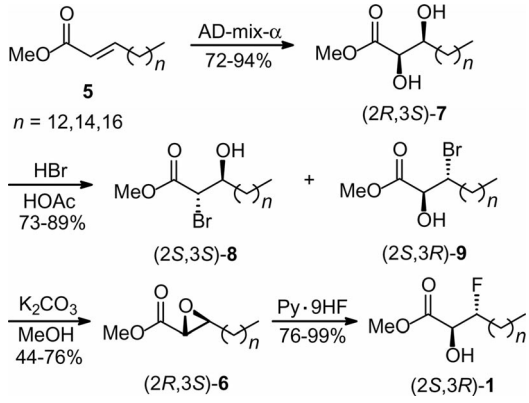
m-chloroperoxybenzoic acid. The latter compounds **5** were prepared from corresponding aldehydes by Wittig reaction with (methoxycarbonylmethylene)triphenylphosphorane.[10] Treatment of compounds *rac*-**6** with Olah's reagent resulted in the formation of the diastereomerically pure racemic regioisomers *anti*-**1**. A plausible mechanism is outlined in Scheme 1. Initially the strongly acidic fluorination reagent protonates the oxirane ring. The preferred position for the fluoride to open the intermediary cation by back side attack is the β-position because of better stabilization of the partial positive charge due to inductive and resonance effects of the substituents. Related regioselectivity was also observed for the ring opening reaction of epoxides derived from α,β-unsaturated nitriles, esters or amides bearing a phenyl group or two alkyl substituents in β-position.[11]



Scheme 1. Synthesis of the racemic methyl *anti*-3-fluoro-2-hydroxyalkanoates **1**.

However, a free carbenium ion is not likely as an intermediate in the presence of Olah's reagent. More probable, the fluorohydrins were formed via a bridged intermediate associated with hydrogen fluoride following a so-called conveyer-belt mechanism.[12] Thus, the methyl *anti*-3-fluoro-2-hydroxyalkanoates were obtained in 73–80% yields. No other fluorinated compounds were detected in the crude product mixture by ^{19}F NMR spectroscopy.

The corresponding enantiopure (2*S*,3*R*)-3-fluoro-2-hydroxyalkanoates **1** (*anti* isomers) and the diasteromeric methyl (2*S*,3*S*)-3-fluoro-2-hydroxyoctanoate (**3b**, *syn* isomer) were synthesized via two different routes. Several variants of enantioselective epoxidation of α,β-unsaturated esters were shown to be less enantioselective.[13] Thus, Sharpless' dihydroxylation using AD-mix-α was applied to provide the (2*R*,3*S*)-diols **7** in 72–94% yield and 94–97% *ee*. Subsequent treatment with HBr in glacial acetic acid employing the method described by Mori et al.[14] gave mixtures of the regioisomeric bromohydrins (2*S*,3*S*)-**8** and (2*S*,3*R*)-**9**. Depending on the chain length different ratios of the regioisomers were formed (90:10 for *n* = 12; 79:21 for *n* = 14 and 77:23 for *n* = 16). However, no separation was necessary since the (2*R*,3*S*)-epoxides **6** were formed from both regioisomers in 44–76% yields under S_N2 conditions[14] using potassium carbonate at room temperature. Ring opening with Olah's reagent as described above for the racemic epoxides provided the target (2*S*,3*R*)-3-fluoro-2-hydroxy esters **1** as the sole products in 76–99% yields (Scheme 2).

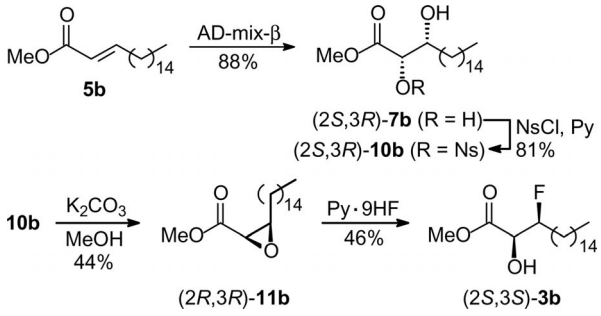


Scheme 2. Synthetic route to the enantiopure (2*S*,3*R*)-3-fluoro-2-hydroxyalkanoates **1**.

In order to prepare methyl (2*S*,3*S*)-3-fluoro-2-hydroxyoctadecanoate (**3b**) (*syn*-configuration) the (2*S*,3*R*)-2,3-diol **7b** obtained from **5b** by Sharpless dihydroxylation[15] using AD-mix-β was esterified selectively at the α-position with nosyl chloride analogous to a protocol described by Matsuura et al.[16] According to the work of Sharpless et al.[17] the introduction of a nosyl- instead of a tosyl group leads to higher regioselectivities, higher yields and better reactivities in the following conversion to epoxides, as described also in other publications.[16,18] In our case the α-hydroxy group was esterified selectively to give the nosylate (2*S*,3*R*)-**10b**, though the reaction did not go to completion (**7b**/**10b** ratio, 1:6, ^{13}C NMR spectroscopically). Unfortunately, compound (2*S*,3*R*)-**10b** decomposed during silica gel chromatography. Therefore epoxide (2*R*,3*R*)-**11b** was directly prepared from the crude nosylate (2*S*,3*R*)-**10b** via an S_N2-reaction by stirring with K_2CO_3 at room temperature and subsequent chromatographic separation from minor amounts of unreacted diol (2*S*,3*R*)-**7b**. The epoxide (2*R*,3*R*)-**11b** was opened using Olah's reagent at 3-position with inversion of the configuration as described above. In this way methyl (2*S*,3*S*)-3-fluoro-2-hydroxyoctadecanoate (**3b**) was obtained in 52% yield (Scheme 3).

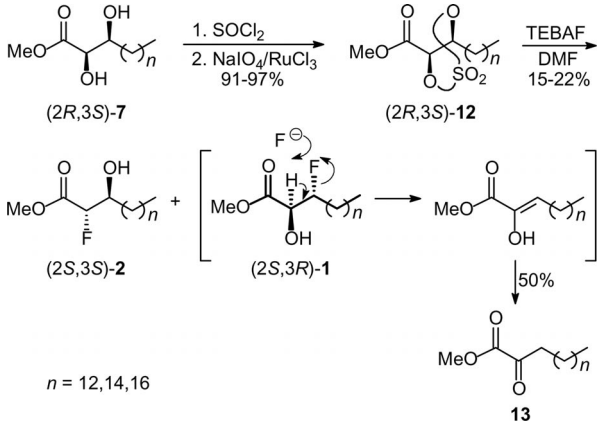
No other fluorinated compound was found in the crude product mixture by ^{19}F NMR spectroscopy. Non-fluorinated impurities were separated chromatographically. In the remaining product the other enantiomer of **3b** could not be detected using the Mosher ester method.[19] Thus the *ee* value is above 98%, so all steps are highly diastereoselective.

The synthesis of the *anti*-regioisomers **2** and the *syn*-regioisomers **4** was designed by opening of the cyclic sulfates (2*R*,3*S*)-**12** or (2*S*,3*S*)-**15**, respectively, with tetrabutylammonium fluoride (TEBAF) through an S_N2 process.[20,21] The sulfates were accessible by two different routes (see



Scheme 3. Synthetic route to methyl (2*S*,3*S*)-3-fluoro-2-hydroxyoctadecanoate (**3b**).

Schemes 4 and 5). The (2*R*,3*S*) isomers **12** were prepared from the corresponding diols (2*R*,3*S*)-**7** in two steps. Opening of these sulfates with TEBAF, as previously discussed in literature[20] for compound **12b**, resulted in the desired *anti*-2-fluoro-3-hydroxy isomers **2**, however as minor components in our cases. The major products were unexpectedly methyl 2-oxoalkanoates **13**. This type of reaction was not previously reported[20] and this mode of reaction was not found either for similar ring opening reactions with other nucleophiles.[15] The reaction might occur due to the strong basicity of fluoride ions in aprotic solvents. A probable mechanism that leads to the formation of compounds **13** from intermediate (2*S*,3*R*)-**1** by fluoride-catalyzed HF elimination is shown in Scheme 4.



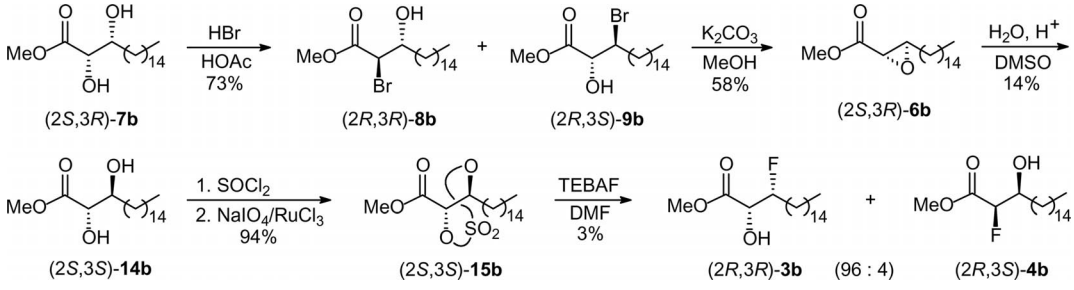
Scheme 4. Formation of methyl (2*S*,3*S*)-2-fluoro-3-hydroxyalkanoates (**2**) and 2-oxo compounds **13**.

A number of different fluorinating reagents such as Bu_4NF, $Bu_4NF{\cdot}3H_2O$, $Me_4NF{\cdot}3H_2O$, $Et_3N{\cdot}3HF$, pyridine·9HF, and KHF_2 were tested as alternative fluoride sources in several solvents (acetone, DMF, DMSO, CH_2Cl_2) in order to improve the regioselectivity of the ring opening and hence the yields of products (2*S*,3*S*)-**2**. Also the work-up conditions were changed, but no improvement of the yield was possible.[22] However, compound (2*S*,3*R*)-**1** was formed as a stable compound under the acidic conditions of epoxide ring opening with pyridine·9HF (see above).

The other diastereomer, (2*R*,3*S*)-2-fluoro-3-hydroxyoctadecanoate (**4b**), was designed to be synthesized analogously from the diastereomeric cyclic sulfate (2*S*,3*S*)-**15b** (Scheme 5).

Consequently, diol (2*S*,3*R*)-**7b** was treated with HBr in glacial acetic acid to give a mixture of the bromohydrins (2*R*,3*R*)-**8b** and (2*R*,3*S*)-**9b**, which on treatment with potassium carbonate gave epoxide (2*S*,3*R*)-**6b**. The subsequent acid-catalyzed hydrolytic ring opening did not proceed smoothly and gave only a low yield of the (2*S*,3*S*)-2,3-diol **14b** in aqueous DMSO at elevated temperature.[23,24] The 2-oxo derivative **13b** was the major product under these conditions. Variation of the reaction conditions did not improve the yield. Then the cyclic sulfate (2*S*,3*S*)-**15b** was accessible from (2*S*,3*S*)-**14b** in two steps with thionyl chloride in dichloromethane according to the method of He et al.[25] and subsequent perruthenate oxidation (94% overall yield). Treatment of sulfate (2*S*,3*S*)-**15b** with TEBAF in DMF gave the expected methyl (2*R*,3*S*)-2-fluoro-3-hydroxyoctadecanoate (**4b**) in low yield. Its regioisomer methyl (2*R*,3*R*)-3-fluoro-2-hydroxyoctadecanoate (**3b**) was formed as the major product with an inversion of configuration at C-3 (Scheme 5). Compound **4b** was isolated by repeated column chromatography.

In contrast to the situation in cyclic sulfate (2*R*,3*S*)-**12b**, the 2-position of diastereomer (2*S*,3*S*)-**15b** seems less accessible towards an S_N2-like fluoride attack. Consequently, (2*R*,3*S*)-**4** is formed as the minor product with (2*R*,3*R*)-**3b**. In contrast to its diastereomer (2*S*,3*R*)-**1**, no HF elimination from (2*R*,3*R*)-3-fluoro-2-hydroxyoctadecanoate (**3b**)



Scheme 5. Synthesis of methyl (2*R*,3*R*)-3-fluoro-2-hydroxyoctadecanoate (**3b**) and methyl (2*R*,3*S*)-2-fluoro-3-hydroxyoctadecanoate (**4b**).

was observed in the reaction of (2*S*,3*S*)-**15b** with TEBAF, maybe due to the disfavored *anti*-conformation of fluorine and hydrogen needed for an E2 process. Thus, both enantiomers of **3b** were prepared from the same diol (2*S*,3*R*)-**7b** with high regioselectivity.

Conformations of Regio- and Stereoisomeric Methyl 2,3-Fluorohydroxyalkanoates

In order to prove the *anti*-configuration of the methyl 3-fluoro-2-hydroxyalkanoates (**1**) prepared from the *trans*-epoxides **6**, the NMR spectra in toluene of the C_{18}-fluorohydrin **1b** was studied and the $^3J_{HF}$ coupling constants were compared to those calculated (SCS-MP2, relative energies and B3LYP-computed *J* values, vide infra) for the mixture of the most stable conformers of methyl *anti*- and *syn*-3-fluoro-2-hydroxybutanoates as model compounds for the long-chain compounds **1** and **3** (Table 1).

Table 1. Temperature dependency of $^3J_{HF}$ coupling constants of the methyl *anti*- and *syn*-3-fluoro-2-hydroxyalkanoates in toluene.

3-Fluoro-2-hydroxy compounds	Coupling constants $^3J_{HF}$ 253 K	293 K	353 K
(3*S*,3*R*)-**1b**, measured[a]	19.2 Hz	18.4 Hz	17.4 Hz
calculated (*anti*)[b]	14.9 Hz	14.8 Hz	14.6 Hz
(2*S*,3*S*)-**3b**, measured[c]	–	31.4 Hz[d]	–
calculated (*syn*)[e]	–	27.4 Hz	–

[a] Determined from the ^{1}H NMR spectra (600 MHz) of (3*S*,3*R*)-**1b**. [b] Average value for the three most stable conformers (see Table 2) at the given temperatures. [c] No temperature effect is expected because similar coupling constants are expected for both conformations. [d] Measured for (2*S*,3*S*)-**3b**. [e] Average value for the two most stable conformers with a ratio of 89.9%: 10.1% at 293 K, see Table 2.

Comparison of the values calculated for the model compounds (Table 1) with the experimental ones suggested the correct assignment as the *anti* isomer **1b** as well as for the *syn* isomer (2*S*,3*S*)-**3b**. Expecting very small effects, we also determined the temperature dependency of the coupling constants for **1b**. Indeed, slightly increasing values were found with decreasing temperature for the $^3J_{HF}$ coupling (Table 1), which is in agreement with the *anti*-configuration. Also the $^3J_{HH}$ of 3.2 Hz calculated for the equilibrium of the three most stable conformers (Table 2) of methyl *anti*-3-fluoro-2-hydroxybutanoate as a model compound is in good agreement with the 3.5 Hz measured for compound **1b**.

The most stable conformations[26–32] of the *syn*- and *anti* isomers of methyl 3-fluoro-2-hydroxybutanoates, the model compounds for **1** and **3**, are shown in Figure 1 and Figure 2, respectively. In the case of the *anti* isomers all energetically low-lying structures have an O–H···O=C hydrogen bond with H···O distances in the range 207–212 pm. This also holds for conformer **A** of the *syn*-form. The second lowest energy structure **B** (about 5.4 kJ/mol) has a relatively short (263 pm) O–H···F–C contact indicating a quite weak hydrogen bond.

Table 2. Calculated[a] energy differences Δ*E* (kJ/mol), populations (percentage at 293 K in parentheses), $^3J_{HF}$ and $^3J_{HH}$ (in Hz) for different conformers of methyl *anti*- and *syn*-3-fluoro-2-hydroxybutanoates.

Conf.	Δ*E* B3LYP	Δ*E* B3LYP	Δ*E* SCS-MP2		
mer	(ε = 1)	(ε = 2.4)	(ε = 2.4)	$^3J_{HF}$	$^3J_{HH}$
anti					
A	0.52 (33.4)	0.00 (41.9)	0.00 (44.1)	14.9	2.2
B	1.20 (25.4)	1.08 (26.9)	0.78 (31.2)	26.6	0.8
C	0.00 (41.2)	0.72 (31.2)	1.35 (24.7)	–0.4	7.7
syn					
A	0.00 (92.7)	0.00 (90.2)	0.00 (89.9)	27.7	2.0
B	6.56 (7.3)	5.36 (9.8)	5.39 (10.1)	25.1	1.2

[a] Single-point energies in the gas phase (ε = 1) and in solution using the COSMO continuum solvation model at a dielectric constant of ε = 2.4 (toluene). The TZV(2df,2pd) AO basis set and B3LYP (ε = 1) optimized structures are employed. The coupling constants were calculated at the B3LYP/TZV(d,p) level.

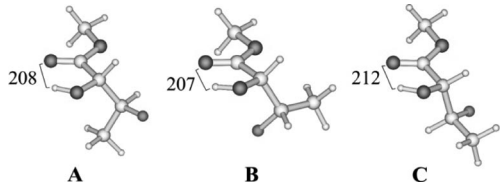


Figure 1. Calculated [B3LYP/TZV(2df,2pd)] most stable conformers of methyl *anti*-3-fluoro-2-hydroxybutanoate. Short intramolecular O–H···O=C contacts are given in pm.

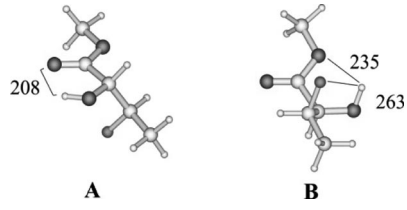


Figure 2. Calculated [B3LYP/TZV(2df,2pd)] most stable conformers of methyl *syn*-3-fluoro-2-hydroxybutanoate. Short intramolecular O–H···O=C/F–C contacts are given in pm.

The relative energies and corresponding Boltzmann populations of the various conformers are given in Table 2. In addition to the standard DFT-B3LYP method, results from the recently developed improved Møller–Plesset perturbation theory (SCS-MP2[33]) were taken into account. All data have been obtained by approximate inclusion of solvent effects via the COSMO continuum solvation model.[34] This is of particular importance especially for the *anti* isomer where the energy differences are only around 1 kJ/mol. Furthermore, in this case the energetic ordering changes when going from the gas phase (**C** is most stable) to toluene solution (**A** is most stable).

The calculated (B3LYP/TZV(d,p)[35]) $^3J_{HF}$ and $^3J_{HH}$ coupling constants are given in Table 2. These calculations are fully analytic and include beside the most important Fermi-contact term also the diamagnetic spin-orbit, paramagnetic spin-orbit, and spin-dipole contributions; for details and further references see ref.[36] For the conformer **C** we obtain

a tiny $^3J_{HF}$ value of –0.4 Hz, while large positive values for **A** (14.9 Hz) and **B** (26.6 Hz) were calculated (at 293 K, see Table 2). The average value of 14.77 Hz for these three conformers compares favorably with the experimental number of 18.4 Hz obtained for methyl (3*S*,3*R*)-3-fluoro-2-hydroxyicosanoate (**1b**), while 27.4 Hz was calculated for the equilibrium of conformers **A** and **B** of the methyl *syn*-3-fluoro-2-hydroxybutanoate. This value is in good agreement with the value of 31.4 Hz measured for (2*R*,3*R*)-**3b**.

The temperature dependence of the coupling constant can be estimated by considering the temperature dependence of the populations of the different conformers according to a Boltzman distribution. For the *anti*-3-fluoro-2-hydroxy isomer (model for compounds **1**) the averaged $^3J_{HF}$ values at the B3LYP level are 13.24 (253 K), 13.28 (293 K) and 13.34 (353 K) Hz. With the SCS-MP2 relative energies and derived populations we obtain 14.90 (253 K), 14.77 (293 K) and 14.61 Hz (353 K) (Table 1). The larger coupling constants and the direction of temperature dependence as computed by SCS-MP2 are in better agreement with experiment indicating the higher quality of the SCS-MP2 compared to the B3LYP energetic description which differs in the ordering of conformers **B** and **C**. For the *syn* isomer (model for compounds **3**) the temperature dependence is insignificant because both contributing species almost have the same coupling constant.

A similar conformational analysis of low energy conformers has been performed for the diastereomeric methyl 2-fluoro-3-hydroxybutanoates, the models for compounds **2** or **4**, respectively. In these cases no temperature-dependent NMR spectra were recorded because of several energetically very similar conformations. The energy differences/populations and plots of the most stable structures are given in Table 3 and Figures 3 and 4, respectively. As noted before, inclusion of a solvation model is crucial to obtain conclusive answers as in the gas phase, for the *anti* isomer only one conformer is dominating. As can be seen from the data in Table 3, compared to the 3-fluoro-2-hydroxybutanoates, there are even more conformers quite close in energy (i.e. four and five vs. three and two). One of the reasons for the different behavior are the more favorable O–H···F–C interactions in the 2-fluoro-3-hydroxybutanoates (i.e. for the *syn*-form, four out of five conformers show short O–H···F–C contacts) compared to the preferred C=O···H–O bridges found in the 3-fluoro-2-hydroxybutanoates. The predicted populations are very similar for B3LYP and SCS-MP2 methods although it is noted that they differ by the lowest energy conformer (*anti*: **A** with B3LYP and **B** with SCS-MP2, *syn*: **A** with B3LYP and **D** with SCS-MP2).

Table 3. Calculated[a] energy differences ΔE (kJ/mol) and populations (percentage at 293 K in parentheses), $^3J_{HF}$ and $^3J_{HH}$ (in Hz) for different conformers of methyl *anti*- and *syn*-2-fluoro-3-hydroxybutanoates.

Conf.	ΔE B3LYP (ε = 2.4)	ΔE SCS-MP2 (ε = 2.4)	$^3J_{HF}$	$^3J_{HH}$
anti				
A	0.00 (47.8)	0.50 (24.8)	–1.1	7.5
B	2.00 (20.7)	0.00 (30.6)	17.3	2.4
C	2.00 (21.0)	0.46 (25.2)	21.7	2.8
D	3.64 (10.5)	1.10 (19.4)	17.8	2.0
syn				
A	0.00 (32.5)	0.43 (26.5)	20.4	1.2
B	2.20 (13.3)	2.52 (11.2)	11.5	7.0
C	1.83 (15.5)	1.82 (14.9)	5.9	4.9
D	0.62 (25.6)	0.00 (31.9)	21.1	1.6
E	2.23 (13.1)	1.73 (15.5)	13.8	6.7

[a] Single-point energies using the COSMO continuum solvation model at a dielectric constant of ε = 2.4 (toluene). The TZV(2df,2pd) AO basis set and B3LYP (ε = 1) optimized structures are employed.

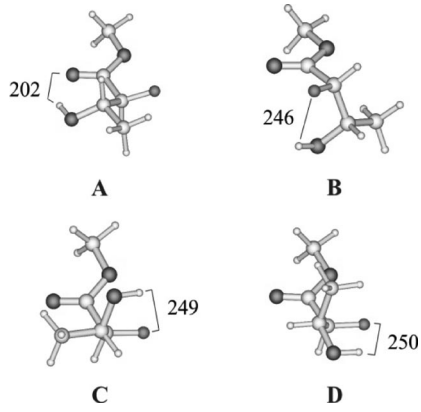


Figure 3. Calculated [B3LYP/TZV(2df,2pd)] most stable conformers of methyl *anti*-2-fluoro-3-hydroxybutanoate. Short intramolecular O–H···O=C/F–C contacts are given in pm.

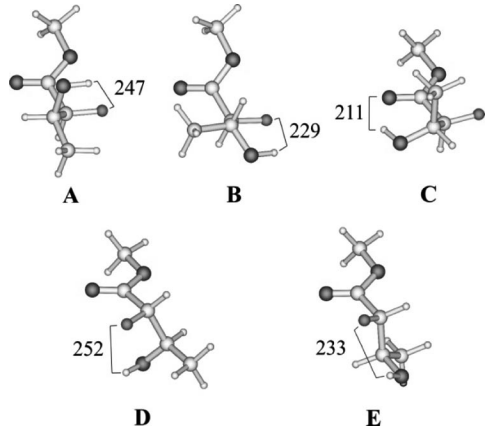


Figure 4. Calculated [B3LYP/TZV(2df,2pd)] most stable conformers of methyl *syn*-2-fluoro-3-hydroxybutanoate. Short intramolecular O–H···O=C/F–C contacts are given in pm.

Conclusions

All regioisomeric and diastereoisomeric methyl *anti*- and *syn*-2,3-fluorohydroxyalkanoates with C_{16}, C_{18}, and C_{20} chains were synthesized in diastereomerically and enantiomerically pure form. While S_N1-like ring opening of *cis*- or *trans*-2,3-epoxides with pyridine·9HF lead selectively to the 3-fluoro-2-hydroxyalkanoates, the S_N2-like ring opening of cyclic sulfates derived from the corresponding 2,3-diols with

the more nucleophilic tetrabutylammonium fluoride lead to the 2-fluoro-3-hydroxyalkanoates in low yields, probably due to steric constraints of the 2-position. The lowest energy conformations of these compounds have been estimated by quantum chemical calculations [B3LYP/TZV(2df,2pd)] on shorter-chain homologues. All three almost equally stable conformations of methyl *anti*-3-fluoro-2-hydroxybutanoate are mostly determined by strong hydrogen bonds of the OH group to the carbonyl oxygen characterized by quite short distances of 2.08 Å (**A**), 2.07 Å (**B**), and 2.12 Å (**C**). The OH group and fluorine are in a *gauche* position in conformers **A** and **B**, but lacking any close O–H···F–C contact. In conformer **C** these two groups are in *anti* position. Similarly, also conformation **A** of the *syn* isomer is determined by strong interaction of the OH and the C=O groups. Only in the less stable conformer *syn*-**B** a weak hydrogen bond stabilizes this arrangement. In contrast, all conformers of methyl *anti*-2-fluoro-3-hydroxybutanoate and four out of five of its *syn* isomer are stabilized by weak O–H···F–C hydrogen bonds exhibiting short H···F distances, well below the sum of the van-der-Waals radii of 267 pm. Also, the most stable conformations of 2-fluoroethanol, 2-fluoropropanol and 3-fluorobutan-2-ol in liquid phase are those with fluorine *gauche* to oxygen[37,38] giving rise to the formation of hydrogen bonds, which was proved by experimental results[39–42] and theoretical calculations.[2a,3,43,44] The question of whether the fluorine *gauche* effect, which is responsible for the higher stability of the *gauche*- over the *anti*-1,2-difluoroethane,[45] significantly influences the relative energy of vicinal fluorohydroxy compounds will possibly be answered by our further investigations.

Experimental Section

Synthesis of Methyl *trans*-Alk-2-enoates 5: Methyl hexadec-2-enoate, methyl octadec-2-enoate and methyl icos-2-enoate were synthesized by Wittig reaction of the corresponding aldehydes and (methoxycarbonylmethylene)triphenylphosphorane. The phosphorane was synthesized from methyl bromoacetate. Tetradecanal, hexadecanal, and octadecanal were obtained by Swern oxidation of the corresponding alcohols. All conversions followed standard procedures. The measured physical constants and spectroscopic data agree with those given in literature for (methoxycarbonylmethylene)triphenylphosphorane (^{1}H NMR,[46] ^{13}C NMR,[47] GC/MS[48]), tetradecanal (^{1}H NMR,[10c,49] ^{13}C NMR,[10c] GC/MS[10c]), hexadecanal (^{1}H NMR,[10c,50] ^{13}C NMR,[10c,50,51] GC/MS[10c]), octadecanal,[10,52] methyl hexadec-2-enoate,[10c] methyl octadec-2-enoate,[10b,10c] and methyl eicos-2-enoate.[10c]

Methyl *trans*-2,3-Epoxyalkanoates 2: The racemic epoxides were prepared from the corresponding α,β-unsaturated esters **5** using *m*-chloroperoxybenzoic acid in refluxing CH_2Cl_2. The physical constants and spectroscopic data obtained agree with those given in the literature for methyl *trans*-2,3-epoxyhexadecanoate,[10c] methyl *trans*-2,3-epoxyoctadecanoate,[10c] and methyl *trans*-2,3-epoxyicosanoate.[10c]

Synthesis of Methyl (2*R*,3*S*)- and (2*S*,3*R*)-2,3-Dihydroxyalkanoates 7: The diols were synthesized from the corresponding α,β-unsaturated esters **5** by Sharpless dihydroxlylation using the commercially available AD-mix-α for (2*R*,3*S*)-**7** or AD-mix-β for (2*S*,3*R*)-**7**. The physical constants and spectroscopic data obtained for the products agree with those given in literature for methyl (2*R*,3*S*)-2,3-dihydroxyhexadecanoate,[10c] methyl (2*R*,3*S*)-2,3-dihydroxyoctadecanoate,[10c] methyl (2*S*,3*R*)-2,3-dihydroxyoctadecanoate[10c] and methyl (2*R*,3*S*)-2,3-dihydroxyicosanoate.[10c]

Synthesis of the Bromohydrins 8 and 9

Analogously to the published procedure[14] a solution of the corresponding diol (1.0 equiv.) was dissolved in HBr (33% in glacial acetic acid, 3.6 equiv.) and stirred for 1 h at 45 °C. Then methanol was added and the mixture was heated at the indicated temperature for another 12 h. After cooling to room temp. the solution was poured into ice-water and neutralized with $NaHCO_3$. The aqueous phase was extracted with diethyl ether (3 × 50 mL) and dried with $MgSO_4$. Removal of the solvent gave the corresponding bromohydrins as white solids.

Synthesis of Cyclic Sulfates 12: Similar to a published procedure,[20] to an argon-covered solution of the corresponding diol **7** (1 equiv.) in CCl_4 thionyl chloride (1.2 equiv.) was added and the reaction mixture was refluxed. Then the solvent was evaporated completely. The residue was dissolved in CCl_4 and CH_3CN (5 mL each). $NaIO_4$ (1.5 equiv.), $RuCl_3 \cdot 3H_2O$ (1 mol-%) and water (7.5 mL) were added and the solution was stirred at room temperature until the starting material was consumed (DC). After adding of diethyl ether (50 mL) the two layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with water, saturated $NaHCO_3$ and brine and then dried with $MgSO_4$. Removal of the solvent gave the cyclic sulfates as white solids.

Synthesis of Methyl *anti*-3-Fluoro-2-hydroxyalkanoates 1: In a dry polypropylene flask Olah's reagent (10 equiv.) was cooled to 0 °C. Then the corresponding epoxide **6** or **11** (1 equiv.) dissolved in CH_2Cl_2 was carefully added. After reaching room temperature the solution was stirred for another 6 h. The reaction mixture was then poured into ice-cooled 2 M ammonia and neutralized with concentrated ammonia. The organic layer was separated and the aqueous layer was extracted three times with small portions of CH_2Cl_2. The combined organic layer was dried with $MgSO_4$. Removal of the CH_2Cl_2 gave the fluorohydrins as white solids.

Methyl *anti*-3-Fluoro-2-hydroxyhexadecanoate (*rac*-1a): Olah's reagent (0.5 mL, 15.0 mmol), the epoxide *rac*-**6a** (0.43 g, 1.5 mmol), CH_2Cl_2 (2 mL); yield 0.32 g (73%) after column chromatography (cyclohexane/ethyl acetate, 10:1); m.p. 50 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.86 (t, J = 6.7 Hz, 3 H), 1.20–1.36 (m, 22 H), 1.41–1.89 (m, 2 H), 3.14 (d, J = 6.5 Hz, 1 H), 3.81 (s, 3 H), 4.32 (ddd, J = 18.3, J = 6.2, J = 3.5 Hz, 1 H), 4.64 (dddd, J = 47.6, J = 9.2, J = 3.4, J = 3.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.0 (q), 22.6 (t), 25.0 (dt, J = 2.6 Hz), 29.2 to 29.6 (8t), 30.0 (dt, J = 21.4 Hz), 31.9 (t), 52.7 (q), 72.6 (dd, J = 23.1 Hz), 94.4 (dd, J = 177.3 Hz), 172.0 (d, J = 8.7 Hz) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –191.2 (dddd, J = 66.1, J = 17.6, J = 17.6, J = 17.6 Hz) ppm. GC-MS m/z (%) = 304 (0.1) [M$^+$], 284 (3), 269 (0.5), 266 (1), 252 (2), 225 (34), 214 (2), 130 (9), 103 (10), 90 (76), 43 (100). $C_{17}H_{33}FO_3$ (304.4): calcd. C 67.07, H 10.93; found C 67.19, H 10.95.

Methyl *anti*-3-Fluoro-2-hydroxyoctadecanoate (*rac*-1b): Olah's reagent (0.4 mL, 12.0 mmol), the epoxide *rac*-**6b** (0.37 g, 1.2 mmol), CH_2Cl_2 (1.5 mL); yield 0.30 g (75%) after column chromatography (cyclohexane/ethyl acetate, 10:1); m.p. 57 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.21–1.36 (m, 26 H), 1.41–1.89 (m, 2 H), 3.01 (d, J = 6.8 Hz, 1 H), 3.83 (s, 3 H), 4.34 (ddd, J = 18.4, J = 6.6, J = 3.4 Hz, 1 H), 4.65 (dddd, J = 47.4, J = 9.3,

J = 3.4, J = 3.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.1 (q), 22.7 (t), 25.0 (dt, J = 4.0 Hz), 29.2 to 29.6 (10t), 30.0 (dt, J = 19.5 Hz), 31.9 (t), 52.7 (q), 72.7 (dd, J = 22.8 Hz), 94.4 (dd, J = 176.6 Hz), 172.0 (d, J = 9.1 Hz) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –191.9 (dddd, J = 64.9, J = 16.6, J = 16.6, J = 16.6 Hz) ppm. GC-MS m/z (%) = 332 (0.5) [M^+], 312 (3), 294 (4), 280 (12), 253 (100), 242 (13), 130 (38), 103 (37), 90 (100). $C_{19}H_{37}FO_3$ (332.5): calcd. C 68.63, H 11.22; found C 68.43, H 11.23.

Methyl *anti*-3-Fluoro-2-hydroxyicosanoate (*rac*-1c): Olah's reagent (0.5 mL, 15.0 mmol), the epoxide *rac*-**6c** (0.51 g, 1.5 mmol), CH_2Cl_2 (2.0 mL); yield 0.42 g (80%) after column chromatography (pentane/Et_2O, 30:1); m.p. 64 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.21–1.36 (m, 30 H), 1.41–1.89 (m, 2 H), 3.01 (d, J = 6.0 Hz, 1 H), 3.83 (s, 3 H), 4.34 (dm, J = 17.8 Hz, 1 H), 4.65 (dddd, J = 47.4, J = 9.3, J = 3.5, J = 3.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 14.1 (q), 22.7 (t), 25.0 (dt, J = 4.3 Hz), 29.2 to 29.7 (12t), 30.0 (dt, J = 19.3 Hz), 31.9 (t), 52.7 (q), 72.7 (dd, J = 22.8 Hz), 94.5 (dd, J = 176.4 Hz), 172.0 (d, J = 8.8 Hz) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –191.9 (dddd, J = 65.7, J = 17.0, J = 17.0, J = 17.0 Hz) ppm. GC-MS m/z (%) = 360 (0.1) [M^+], 340 (23), 322 (3), 308 (5), 281 (92), 270 (6), 130 (21), 103 (20), 90 (100). $C_{21}H_{41}FO_3$ (360.6): calcd. C 69.96, H 11.46; found C 69.88, H 11.50.

Methyl (2*S*,3*R*)-3-Fluoro-2-hydroxyhexadecanoate (1a): Epoxide (2*R*,3*S*)-**6a** (1.53 g, 5.4 mmol), purified on silica gel (cyclohexane/ethyl acetate, 10:1); yield 1.45 g (88%); m.p. 50 °C. $[\alpha]_D^{20}$ = –5.6 (c = 1.02, $CHCl_3$).

Methyl-(2*S*,3*R*)-3-Fluoro-2-hydroxyoctadecanoate (1b): Epoxide (2*R*,3*S*)-**6b** (0.37 g, 1.2 mmol) purified on silica gel (cyclohexane/ethyl acetate, 10:1); yield 0.30 g (76%); m.p. 57 °C. $[\alpha]_D^{20}$ = –8.4 (c = 1.01, $CHCl_3$).

Methyl (2*S*,3*R*)-3-Fluoro-2-hydroxyicosate (1c): Epoxide (2*R*,3*S*)-**6c** 0.10 g (0.3 mmol) purified on silica gel (cyclohexane/ethyl acetate, 10:1); yield 0.11 g (99%); m.p. 64 °C. $[\alpha]_D^{20}$ = –3.4 (c = 1.01, $CHCl_3$).

Methyl (2*S*,3*S*)-3-Fluoro-2-hydroxyoctadecanoate (3b): Olah's reagent (0.6 mL, 18 mmol), the epoxide (2*S*,3*S*)-**11b** (0.624 g, 2.0 mmol), CH_2Cl_2 (9 mL); yield 0.348 g (52%) after column chromatography (cyclohexan/ethyl acetate, 10:1 and 6:1); m.p. 69 °C. $[\alpha]_D^{20}$ = –12.0 (c = 1.01, $CHCl_3$), >98% *ee* (determined by Mosher's ester). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.6 Hz, 3 H), 1.22–1.36 (m, 26 H), 1.42–1.52 (m, 2 H), 2.17 (s, 1 H), 3.85 (s, 3 H), 4.16 (dd, J = 1.6, J = 30.6 Hz, 1 H), 4.76 (ddt, J = 1.6, J = 46.9, J = 10.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.1 (CH_3), 22.7 (CH_2), 25.0 (CH_2), 29.3 to 29.7 (10 CH_2), 30.5 (d, J = 20.8 Hz, CH_2), 32.0 (CH_2), 52.9 (CH_3), 72.0 (d, J = 21.2 Hz, CH), 93.0 (d, J = 175.8 Hz, CH), 172.4 (d, J = 3.4 Hz, 1 C) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –195.6 (dddd, J = 46.9, J = 30.4, J = 17.1, J = 13.3 Hz) ppm. HRMS (ESI) m/z: calcd. for $C_{19}H_{37}FO_3Na$ 335.2619; found 335.2619.

Synthesis of the Methyl 2-Fluoro-3-hydroxyalkanoates (2*S*,3*S*)-2 and (2*R*,3*S*)-4: To a solution of the corresponding cyclic sulfate (2*S*,3*S*)-**12** or (2*R*,3*S*)-**15** in DMF, Bu_4NF (> 2 equiv.) was given and stirred at room temperature till no starting material was detected anymore (DC). The solvent was evaporated and the sticky crude product was dissolved in a 1:1 mixture of Et_2O and H_2SO_4 (20%) and stirred until the spot at R_f = 0 has disappeared. The two layers were separated and the aqueous layer was extracted with a small amount of CH_2Cl_2. The combined organic layer was washed with water and 10% $NaHCO_3$ solution and dried with $MgSO_4$. Removal of the solvent gave crude mixtures of the fluorohydrins **2** and **4** and the α-ketocarboxylic esters **13** as white solids. The desired products **2** and **4** were isolated in >97% purity by repeated careful column chromatography. In order to demonstrate the identity of the α-ketocarboxylic esters, compound **13b** was isolated chromatographically.

Methyl (2*S*,3*S*)-2-Fluoro-3-hydroxyhexadecanoate (2a): From the sulfate (2*R*,3*S*)-**12a** (0.182 g, 0.5 mmol); yield 0.033 g (22%) after column chromatography (cyclohexane/ethyl acetate, 8:1); m.p. 61 °C. $[\alpha]_D^{20}$ = –6.2 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.21–1.36 (m, 22 H), 1.47–1.63 (m, 2 H), 2.27 (br. s, 1 H), 3.82 (s, 3 H), 3.95–4.10 (dm, J = 17.7 Hz, 1 H), 4.87 (dd, J = 48.4, J = 4.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.0 (q), 22.7 (t), 25.3 (t), 28.9 (t), 29.3 to 29.6 (8t), 31.5 (dt, J = 5.9 Hz), 31.9 (t), 52.4 (q), 71.7 (dd, J = 21.5 Hz), 91.3 (dd, J = 186.8 Hz), 168.5 (d, J = 23.9 Hz) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –199.8 (dd, J = 47.8, J = 17.7 Hz) ppm. GC-MS m/z (%) = 304 (2) [M^+], 303 (8), 289 (0.5), 286 (2), 284 (0.1), 266 (1), 227 (1), 214 (23), 213 (9), 121 (23), 105 (8), 92 (100). HRMS: $C_{17}H_{31}O_2F$ calcd. 286.2308; found 286.2277.

Methyl (2*S*,3*S*)-2-Fluoro-3-hydroxyoctadecanoate (2b): From the sulfate (2*R*,3*S*)-**12b** (0.196 g, 0.5 mmol); yield 0.030 g (18%) after column chromatography (cyclohexane/ethyl acetate, 8:1); m.p. 65 °C. $[\alpha]_D^{20}$ = –5.5 (c = 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.21–1.34 (m, 26 H), 1.48–1.63 (m, 2 H), 3.83 (s, 3 H), 3.95–4.08 (dm, J = 17.6 Hz, 1 H), 4.86 (dd, J = 48.4, J = 3.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.1 (q), 22.7 (t), 25.4 (t), 29.2 to 29.7 (10t), 31.5 (dt, J = 4.7 Hz), 31.9 (t), 52.4 (q), 71.8 (dd, J = 21.4 Hz), 91.3 (dd, J = 186.9 Hz), 168.5 (d, J = 23.4 Hz) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –199.8 (dd, J = 48.2, J = 17.8 Hz) ppm. GC-MS m/z (%) = 333 (0.1) [MH^+], 332 (0.1) [M^+], 331 (0.1) [M^+ – H], 314 (4), 312 (0.1), 294 (1), 279 (0.5), 255 (0.5), 242 (26), 241 (10), 121 (38), 105 (8), 92 (100). HRMS $C_{19}H_{35}O_2F$ calcd. 314.2621; found 314.2629.

Methyl 2-Oxo-octadecanoate (13b): Isolated as the main product of the former reaction by chromatography; yield 0.078 g (50%); m.p. 57 °C (cyclohexane/ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.88 (t, J = 6.7 Hz, 3 H), 1.21–1.41 (m, 26 H), 1.63 (m, 2 H), 3.84 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.0 (q), 22.7 (t), 23.0 (t), 28.9 (t), 29.2 to 29.6 (10t), 31.9 (t), 39.3 (t), 52.7 (q), 161.7 (s), 194.2 (s) ppm. GC-MS m/z (%) = 313 (0.5) [MH^+], 312 (1) [M^+], 331 (0.1) [M^+ – 1], 280 (0.1), 254 (24), 253 (100), 235 (4), 137 (6), 123 (12), 111 (8), 109 (17), 97 (23), 95 (26), 85 (37), 83 (28), 71 (55), 69 (22), 57 (82), 55 (32), 43 (45), 41 (22). $C_{19}H_{36}O_3$ (312.5): calcd. C 73.03, H 11.61; found C 72.94, H 11.47. The ^{13}C NMR spectroscopic data agree with published ones.[53]

Methyl (2*S*,3*S*)-2-Fluoro-3-hydroxyicosanoate (2c): From the sulfate (2*R*,3*S*)-**12c** (0.210 g, 0.5 mmol); yield 0.027 g (15%) after column chromatography (cyclohexane/ethyl acetate, 8:1); m.p. 66 °C. $[\alpha]_D^{20}$ = –3.8 (c = 0.84, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (t, J = 6.9 Hz, 3 H), 1.23–1.36 (m, 30 H), 1.47–1.63 (m, 2 H), 1.80 (br. s, 1 H), 3.85 (s, 3 H), 4.02 (dddd, J = 17.5, J = 8.5, J = 4.3, J = 4.3 Hz, 1 H), 4.88 (dd, J = 48.3, J = 4.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 14.1 (q), 22.7 (t), 25.4 (t), 29.3, 29.4, 29.5, 29.6, 29.7 (12t), 31.5 (dt, J = 4.2 Hz), 31.9 (t), 52.4 (q), 71.8 (dd, J = 21.4 Hz), 91.3 (dd, J = 188.3 Hz), 168.5 (d, J = 23.8 Hz) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –199.8 (dd, J = 47.9, J = 18.1 Hz) ppm. GC-MS m/z (%) = 360 (0.1) [M^+], 342 (8), 340 (0.1), 322 (3), 307 (0.1), 281 (1), 270 (30), 269 (12), 121 (43), 105 (8), 92 (100). HRMS: $C_{21}H_{39}O_2F$ calcd. 342.2934; found 342.2970.

Methyl (2*R*,3*R*)-3-Fluoro-2-hydroxyoctadecanoate (3b): Isolated as major product from the reaction of cyclic sulfate (2*S*,3*S*)-**15b** (0.392 g, 1.0 mmol); yield 0.153g (46%) $[\alpha]_D^{20}$ = +8.4 (c = 0.37,

$CHCl_3$); m.p. 64 °C. The spectroscopic data agree with those of the (2*S*,3*S*)-enantiomer.

Methyl (2*R*,3*S*)-2-Fluoro-3-hydroxyoctadecanoate (4b): Isolated as minor product from the reaction of cyclic sulfate (2*S*,3*S*)-**15b** (0.392 g, 1.0 mmol); yield 0.009g (3%) after repeated column chromatography (cyclohexane/ethyl acetate, 10:1); m.p. 71 °C. $[\alpha]_D^{20}$ = +3.6 (*c* = 0.64, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.88 (t, *J* = 6.4 Hz, 3 H), 1.26 (s, 16 H), 1.66–1.57 (m, 2 H), 3.84 (s, 3 H), 4.09–3.94 (dm, *J* = 24.6 Hz, 1 H), 4.86 (dd, *J* = 2.5, *J* = 48.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 14.1 (CH_3), 22.7 (CH_2), 25.5 (CH_2), 29.3 to 29.8 (8 CH_2), 32.7 (CH_2), 52.5 (CH_3), 71.8 (d, *J* = 20.4 Hz, CH), 90.6 (d, *J* = 188.5 Hz, CH), 168.8 (d, *J* = 24.5 Hz, 1 C) ppm. ^{19}F NMR ($CDCl_3$, 282 MHz): δ = –209.2 (dd, *J* = 48.0, *J* = 24.5 Hz) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{37}FO_3Na$ 355.2619 found: 355.2625.

Supporting Information (see also the footnote on the first page of this article): Experimental remarks, synthetic procedures and spectroscopic data for compounds **6a**–**c**, **8a**–**c**/**9a**–**c**, **10b**, **11b**, **12a**–**c**, **14b**, **15b**, and the NMR spectra for compounds **1**–**15** are available.

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) (SFB 424). We are grateful to the Bayer AG, Leverkusen for the kind donation of chemicals.

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Received: August 30, 2010
Published Online: November 17, 2010

