EPC Syntheses of Trifluorocitronellol and of Hexafluoropyrenophorin – A Comparison of Their Physiological Properties with the Nonfluorinated Analogs

Stephan P. Götzö,[a][1] Dieter Seebach,*[a] and Jean-Jacques Sanglier[b]

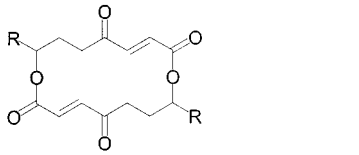
Dedicated to Dr. Günther Ohloff on the occasion of his 75th birthday

Keywords: (*S*)-4,4,4-Trifluoro-3-hydroxybutanoic acid / 2-Trifluoromethyl-3-hydroxypropanoic acid (F_3-*Roche* acid) / Chiral CF_3-containing synthetic building blocks / Natural products / Cyclizations / Olfactory comparison

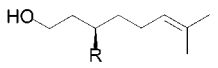
The natural products pyrenophorin (**1a**) and citronellol (**2a**), in which CH_3 groups are replaced by CF_3, were synthesized in enantiomerically pure form from simple four-carbon trifluorohydroxy acids (obtained by resolution). The cyclizations of analogous CH_3 and CF_3 *seco* acids (cf. **9**) to give pyrenophorin derivatives require different methodologies; the F_6 derivative **10a** could be obtained in only very poor yield; in contrast to pyrenophorin. Most surprisingly, F_6-pyrenophorin (**1d**) has an extremely poor solubility in common organic solvents, and has essentially no antimicrobial activity (see Table 2). The synthesis of F_3-citronellol is the first application of an enantiopure F_3-*Roche* acid (**12**) as a synthetic builiding block (see its derivatives **17–23**). An olfactory comparison of F_3-citronellol [(*R*)-(+)-**2b**] with citronellol and *ent*-citronellol (Scheme 6) shows that the fluorine derivative has a "very metallic, aggressive" character and lacks totally the "sweetness" of (*R*)-(+)- and (*S*)-(–)-**2a**. A number of generally useful, CF_3-substituted electrophilic (iodides **4**, **18**, **37**, tosylates **19**, **33**, aldehydes **5**, **29**, **39**) and nucleophilic (Li dithiane precursor of **5**, Li compounds **20**, **38**) reagents are described for the first time.

Introduction

In the course of our work on the preparation of enantiopure F-substituted synthetic building blocks[2] we have made use of classical, large-scale resolution through diastereomeric salt formation to obtain (*R*)- and (*S*)-3,3,3-trifluorolactic acid,[3] 4,4,4-trifluoro-3-hydroxybutanoic acid,[4] and 3-hydroxy-2-(trifluoromethyl)propionic acid (trifluoro *Roche* acid).[5] These chiral starting materials were converted into synthetically useful reagents such as CF_3-substituted Li enolates, organolithium compounds, halides, epoxides, aldehydes, and Michael acceptors. Target structures of syntheses employing these reagents were amino acids and dendrimers. Now, we have demonstrated their usefulness for preparing and testing the CF_3 analogs of two natural products, pyrenophorin and citronellol (**1a** and **2a** in Scheme 1).



1a (R = CH_3, (*R*,*R*) ≡ pyrenophorin)
1b (R = CH_2COCH_3, (*S*,*S*) ≡ vermiculin)
1c (R = H ≡ nor-pyrenophorin)
1d (R = CF_3, (*S*,*S*) ≡ hexafluoro pyrenophorin)



2a (R = CH_3 ≡ (*R*)-citronellol)
2b (R = CF_3)

Scheme 1. Structure of pyrenophorin and citronellol and of the fluoro analogs

(*S*,*S*)-Hexafluoropyrenophorin (1d)

With our experience in the synthesis of macrolide and macrodiolide (cf. **1a**, **b**, **c**) natural products,[6] we chose pyrenophorin as a target molecule to compare the synthesis and the activity of fluorinated (**1d**) and nonfluorinated antibiotics (**1a**).[7] The synthetic route was analogous to the one we had used for natural pyrenophorin many years ago:[8][9] Ethyl 3-hydroxy-4,4,4-trifluorobutanoate[4] was protected by *tert*-butyldimethylsilylation and reduced to the alcohol **3**[10] which, in turn, was converted into the iodide **4**. 2-Lithio-1,3-dithiane was then alkylated by this iodide and formylated in situ (DMF) to give the aldehyde **5**. Olefination with methoxycarbonylmethylenetriphenylphosphorane (→ **6**) and saponification or desilylation gave the half-protected *seco*-acid derivatives **7** and **8**, respectively,[11] and desilylation of the acid **7** provided the hydroxy acid **9**.[12]

Pyrenophorin (**1a**), its acetyl derivative vermiculin (**1b**), and norpyrenophorin (**1c**) have been obtained directly from the corresponding hydroxy acids by Mitsunobu macrocy-

[a] Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum,
Universitätstraße 16, CH-8092 Zürich, Switzerland
Fax: (internat.) + 41-1/632-1144
E-mail: seebach@org.chem.ethz.ch
[b] Core Technology Area, Research, Novartis Pharma. Inc.,
CH-4002 Basel
Fax: (internat.) + 41-61/324-3279
E-mail: jeanjacques.sanglier@pharma.novartis.com
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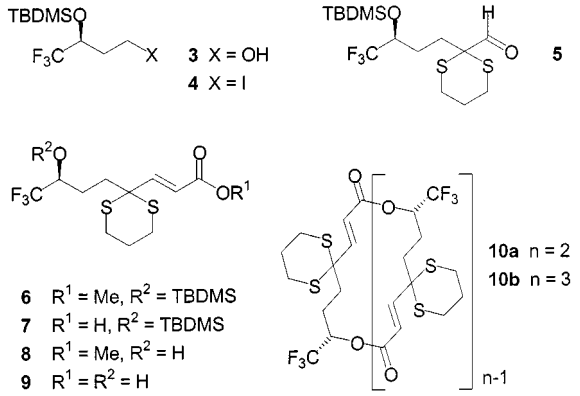


Scheme 2. Building blocks and intermediates used in the synthesis of **1d**

clization methods.[8][9] Since we knew[3][4] that S_N2 substitutions in the α position of a CF_3 group are unfavorable, we tested methods for diolide formation with the acid **9** which involve activation of the acid group (mixed anhydride; activated ester). After extensive experimentation we realized that we could not achieve the cyclization in good yields at all. The best conditions, leading to a ca. 3:1 mixture of the desired diolide **10a** and the corresponding triolide **10b** in a total yield of ca. 12%, turned out to be conversion of acid **9** to the acid chloride with the Ghosez chloro enamine[13] and high-dilution treatment[14] with DMAP in refluxing toluene (see Experimental Section).

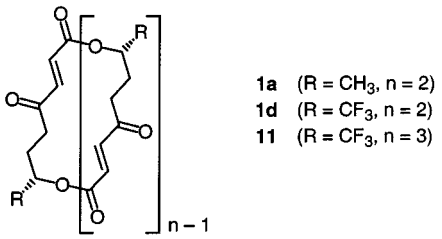
Hydrolytic cleavage of the dithianes in the diolide and triolide **10** with $Hg(ClO_4)_2 \cdot 3\ H_2O$ in THF[15] gave parent compounds **1d** and **11** (47 and 81%, respectively, after purification).[16] We were surprised to find that the F_6-pyrenophorin **1d** is poorly soluble in all common organic solvents[17] and that it has a high melting point with decomposition above 260°C (Table 1). In sharp contrast, the nonfluorinated pyrenophorin is readily soluble and has a m.p. of 175°C. In our previous experiences, F_3-substituted compounds are usually more soluble, lower melting, lower boiling and faster eluting from columns, i.e. less polar and more lipophilic than their nonfluorinated counterparts.[18][19] Also, the triolide **11** was found to have "normal" properties (m.p. 144°C, well soluble in CH_2Cl_2).

Another surprise was encountered when we determined the antimicrobial activity of F_6-pyrenophorine **1d**, in comparison with the nonfluorinated compound **1a** and with the triolide **11**; replacement of the CH_3 groups in **1a** by CF_3 led to complete loss of activity, while the triolide showed some activity (Table 2). It is, of course, impossible to say whether the lack of activity of **1d** is simply due to its poor solubility or to steric or electronic effects in the interaction with the biosystem.

(*R*)-Trifluorocitronellol 2b

A compound with which olfactorial activities of CH_3 and CF_3-substituted analogs could be compared is citronellol **2a**. Thus F_3-citronellol **2b** was chosen as a target molecule,

Table 1. Comparison of the melting points and optical rotations of the fluorinated diolide **1d** and the corresponding triolide **11** with those of pyrenophorin (**1a**)



cmpd.	m.p. (°C)	$[\alpha]_D^{RT}$
1a	175	–54.5 (c = 0.48, acetone)
1d	261–264[a]	–26.9 (c = 0.175, solvent[b])
11	144.4–144.8	+4.9 (c = 0.10, $CHCl_3$)

[a] under decomposition
[b] $CF_3CH(OH)CF_3/CH_2Cl_2$ 1.5:1

Table 2. Antimicrobial activity of the compounds **1a**, **1b**, **1d** and **11**, using agar diffusion tests

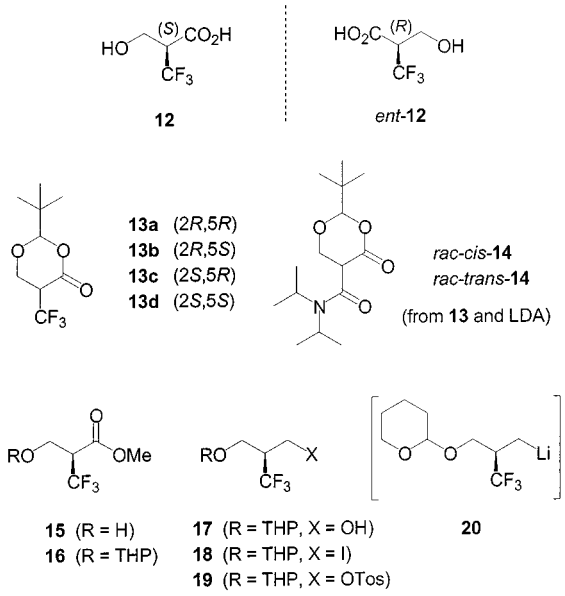
Organisms	Diameter of the area of growth inhibition [mm] at a substrate concentration of 1 mg/ml			
	pyrenophorin (**1a**)	vermiculin (**1b**)	hexafluoropyrenophorin (**1d**)	triolid **11**
Staphylococcus aureus	17	12	+	10
Micrococcus lysodeiktikus	22	0	0	11
Sarcina lutea	18	14	+	9
Comamonas terrigena	0	10	0	9
Saccharomyces cerevisiae	21	0	0	0
Candida albicans	19	0	0	12
Aspergillus niger	18	0	0	0
Neurospora crassa	16	0	0	0

The substances were applied as a solution, **1a** in ethanol, **1b** in DMSO, and **1d** and **11** in warm acetone. + means that the activity was at the limit of detection

for a demonstration of the usefulness of trifluoro *Roche* acid **12** as a chiral starting material, with the additional goal of learning about the reactivity and properties of the intermediates en route from **12** to **2b**.

The *Roche* acid (**12**, CH_3 instead of CF_3) has turned out to be an extremely versatile chiral building block because the two *O*-functionalized carbon atoms reside in the enantiotopic half spaces of the chirality center. This allows the synthetic chemist to prepare either enantiomer of a target compound from *one* enantiomer of this acid.[20] The same is, of course, true of the trifluoro *Roche* acid **12**.[5] The extent to which the CF_3 group would be compatible with reactions which are known to work with the parent CH_3 analog[20] was of interest. One reaction which is prevented by CF_3 is the generation of a neighboring Li-enolate moiety: thus, the dioxanones **13a–d**, prepared as previously described for the CH_3 analogs,[21] when treated with LDA and Mel, gave the *N*,*N*-diisopropylamides **14** as the only ident-

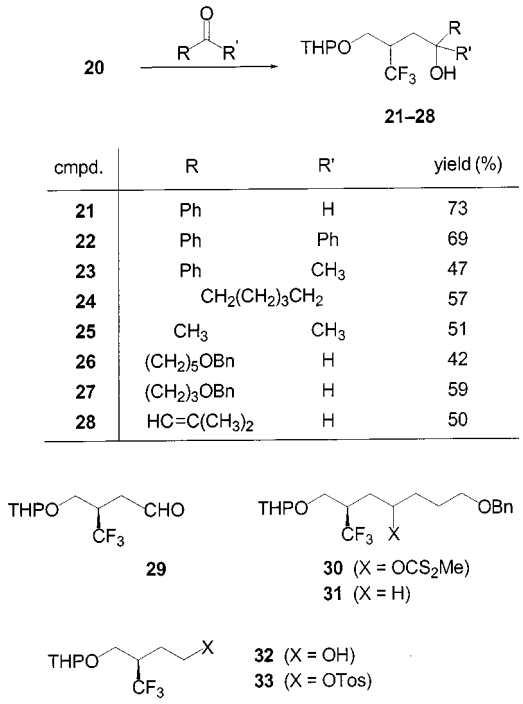
ified products, rather than the 5-methyl-5-(trifluoromethyl)-dioxanone (Scheme 3).[22]



Scheme 3. Trifluoro-*Roche* acid **12** and derivatives **13**, **15**−**20** for synthetic transformations; all THP derivatives shown are mixtures of epimers at the 2-position of the THP ring

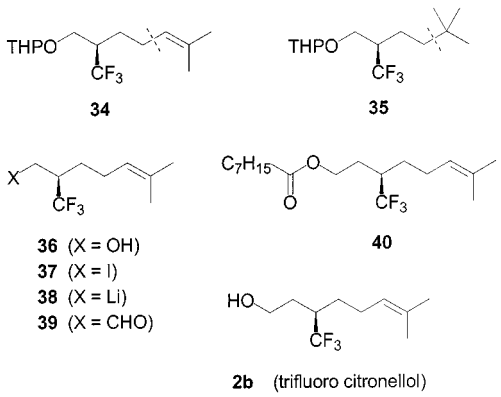
On the other hand, THP protection of the ester **15** (→ **16**), reduction with DIBAH and conversion of the resulting alcohol **17**[23] to the iodide **18**, and I/Li exchange[24][25] gave the reagent **20** which could be used for C−C coupling reactions, such as nucleophilic additions to aldehydes, ketones or DMF (products **21**−**29** in Scheme 4). The stability of ethereal solutions of Li compound **20** at low temperatures is remarkable, if one considers that it could eliminate THPOLi or LiF with formation of three-membered rings, or of THP-protected 2-trifluoromethyl-2-propen-1-ol.[26]

From the CF_3-substituted triol derivative **27** we have removed the secondary OH group by Barton's method[27] to obtain, through the xanthate ester **30**, the THP/Bn-protected diol **31**, a possible precursor to the trifluoro derivative of caprolactin B.[28] Electrophilic reactivity could be realized in the Fouquet−Schlosser coupling[29] of the tosylate **19** with pentyl magnesium bromide [to give ca. 40% of THP-protected 2-(trifluoromethyl)octanol]. Unfortunately, the tosylate **19** did not react with the Grignard reagent from 1-bromo-2-methyl-2-butene to give the citronellol precursor **34**. Thus, we switched to the homologated tosylate **33** (obtained from the aldehyde **29** through the alcohol **32**, which *did* react with the so-called higher order cuprate (from 1-bromo-2-methyl-propene, *t*BuLi[24] and CuCN[30]) to produce a ca. 5:1 mixture of the desired precursor and the *tert*-alkyl derivative **35** (total yield 87%). Unfortunately, we were not able to separate the two compounds **34** and **35**, and therefore decided to carry the mixture through the next steps, hoping for a separation chance at a later stage. As outlined in Scheme 5 (the formulae of intermediates derived from the impurity **35** are not shown), we homologated the alcohol **36** to F_3-citronellol **2b**, via iodide **37**, lithio derivative **38** and aldehyde **39**.



cmpd.	R	R'	yield (%)
21	Ph	H	73
22	Ph	Ph	69
23	Ph	CH_3	47
24	$CH_2(CH_2)_3CH_2$		57
25	CH_3	CH_3	51
26	$(CH_2)_5OBn$	H	42
27	$(CH_2)_3OBn$	H	59
28	$HC{=}C(CH_3)_2$	H	50

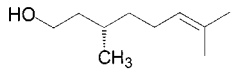
Scheme 4. Products **21**−**29** from Li derivative **20** and carbonyl compounds; the diol and triol derivatives **30**−**33** result from transformations of the aldehyde **29** and of the adduct **27**; the alcohols **21**−**28** were prepared using *rac*-**18**; there is essentially no diastereoselectivity in the formation of the new stereogenic center in **21**, **23**, and **26**−**28**; all THP derivatives shown are mixtures of epimers at the 2-position of the THP ring



Scheme 5. Intermediates **34**, **36**−**40** (and side product **35**) for the synthesis of (*R*)-trifluorocitronellol (**2b**); the derivatives **34** and **35** are epimeric mixtures at the 2-position of the THP ring

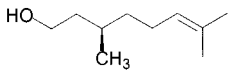
The caprylate **40** of the trifluorocitronellol was separated from the concomitant saturated impurity[31] by a classical method[32] involving the reversible addition of $Hg(OAc)_2$ to the double bond: The adduct formed with **40** is soluble in MeOH, the *tert*-alkyl impurity in isooctane, which allows for a simple extractive separation, followed by elimination with aqueous HCl. The pure caprylate **40** thus isolated was saponified to the citronellol derivative **2b** (total yield from the tosylate **33** ca. 11%). The analytically pure trifluorocitronellol **2b** is a colorless liquid, which was fully characterized ($[\alpha]_D^{r.t.}$, IR, ^{1}H-, ^{13}C-, and ^{19}F-NMR spectroscopy, mass spectrometry, elemental analysis) and used for the ol-

factory comparison with citronellol (*R*)-**2a** and *ent*-citronellol. As described in Scheme 6, the homochiral compound **2a** with CH_3 and **2b** with CF_3 substitution have a totally different fragrance.



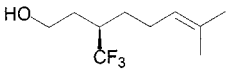
(*S*)-(−)-*ent*-**2a**

Fresh, light, diffuse, typically rosy, slightly waxy, sweet.



(*R*)-(+)-**2a**

Green, floral-rosy, slightly minty, less fresh than (*S*)(−), slightly green.



(*R*)-(+)-**2b**

White flower, lily of the valley, almost not rosy, but very metallic, aggressive, lacks totally the sweetness of the others.

Scheme 6. Olfactory comparison of (*R*)-trifluorocitronellol (**2b**) with citronellol (**2a**) and *ent*-**2a** (also known as β-rhodinol)

This is in contrast to some monofluoro derivatives, comparison of which with the nonfluorinated analogs furnished only minor "olfactive dissimilarities"[33] (cf. also the discussions in the corresponding monographs[2]).

Experimental Section

General: All reactions requiring anhydrous conditions were carried out in flame-dried flasks under a positive pressure of argon. All transfers of solutions and solvents were peformed by syringe techniques or via cannula. CSA = *rac*-10-camphorsulfonic acid; DIBAH = diisobutylaluminum hydride (ca. 1 M in hexane); DMAP = 4-(dimethylamino)pyridine; *er* = enantiomer ratio; GP = General Procedure; HV = High Vacuum (0.01−0.1 Torr); r.t. = room temperature; RV = rotary evaporation. BuLi (ca. 1.5 M in hexane) and *t*BuLi (ca. 1.5 M in pentane) were titrated before use (*sec*-butanol and 1,10-phenantrolin). DMF was distilled from CaH_2 and stored over 4-Å molecular sieves. THF was freshly distilled from K/benzophenone and toluene from Na under argon before use. Solvents for chromatography and workup procedures were distilled from sikkon (anhydrous $CaSO_4$; Fluka). NEt_3 was freshly distilled from CaH_2. Bulb-to-bulb distillation was performed with a Büchi GKR-50; the boiling points given correspond to the temperature of the air bath. − TLC: Merck Kieselgel 60 F_{254} plates; detection: UV absorption at λ = 254 nm and staining with basic $KMnO_4$ [0.5% (m/m) $KMnO_4$ in 1 M NaOH]. − FC: Fluka Silica Gel 60 (40−63 μm) under a pressure of approximately 0.2 bar. − GC: Carlo−Erba Instruments 5160-HRGC with a FS-Lipodex E column (γ-CD, Macherey−Nagel, 50 m × 0.25 mm), injector temp. 220°C, detector temp. 250°C (FID), carrier gas H_2 (1.2 bar), temperature programme 10 min 80°C, 0.5°C min^{-1} until 160°C. − HPLC for analytical purposes: Knauer HPLC machine with a Chiracel OD® column (Daicel Chemical Industries, LTD). − Prep. HPLC: Knaur HPLC machine with a Chiraspher® column (Hibar). − Melting points: Büchi 510 apparatus, uncorrected. − Optical rotations: Perkin−Elmer 241 polarimeter (10 cm, 1 mL cell) at r.t. − Elemental analyses: Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich. − IR spectra: Perkin−Elmer 782 spectrophotometer. − ^1H NMR: Bruker AMX-II-500 (500 MHz), Bruker AMX 400 (400 MHz), Bruker ARX 300 (300 MHz), Varian Gemini 300 (300 MHz) or Varian Gemini 200 (200 MHz); $CDCl_3$ was used as solvent and as internal reference (δ = 7.26) unless otherwise stated. − ^{13}C NMR: Bruker AMX-II (125 MHz) or Bruker AMX 400 (100 MHz); $CDCl_3$ was used as solvent and TMS as internal reference (δ = 77.0) unless otherwise stated. − ^{19}F NMR: Varian Gemini 300 (282 MHz); $CDCl_3$ was used as solvent and $CFCl_3$ as internal reference (δ = 0) unless stated otherwise. *J* values are given in Hz. − Mass spectra: VG Tribrid (EI) or Hitachi−Perkin−Elmer RMU-6M (FAB) or Bruker Reflex MALDI-TOF spectrometer. The spectroscopic data of compounds **21**−**28** are available as Supporting Information.

(*S*)-3-*tert*-Butyldimethylsiloxy-4,4,4-trifluorobutan-1-ol (3): A solution of (*S*)-4,4,4-trifluoro-3-hydroxybutanoic acid (55.8 g, 0.353 mol) in EtOH (350 mL) was treated with trimethylsilyl chloride (48 mL, 0.490 mol) and stirred for 2 d at r.t. The solvent was then removed and the residue distilled (83°C/25 mbar) to give ethyl (*S*)-4,4,4-trifluoro-3-hydroxybutanoate (56.9 g, 87%) as a colorless and enantiomerically pure liquid (GC). − $[\alpha]_D^{r.t.}$ = −18.43 (*c* = 2.85, $CHCl_3$). − GC: 0.1% sol. in Et_2O, column FS-Lipodex E, T_{start} 80°C, heating rate 0.5°C min^{-1}, *p* = 1.2 bar, time of retention: [(*S*)-ester] 17.28 min. Further analytical data correspond to those in ref.[4] A solution of the (*S*)-ethyl ester (20.1 g, 108 mmol) in DMF (40 mL) was treated at 0°C with imidazole (18.3 g, 270 mmol) and *tert*-butyldimethylsilyl chloride (19.5 g, 130 mmol). The mixture was stirred at 0°C for 15 min and then at r.t. overnight. After addition of pentane (300 mL) and washing with water (2 × 50 mL), the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by FC (pentane/Et_2O, 19:1) yielded the colorless silylated ester (33.2 g, quant.). − R_f (pentane/Et_2O, 19:1) = 0.61. − ^1H NMR (300 MHz): δ = 0.09 (s, 3 H, MeSi), 0.13 (s, 3 H, MeSi), 0.87 (s, 9 H, *t*Bu), 1.28 (t, *J* = 7.2, 3 H, CH_3), 2.56−2.71 (m, 2 H, 2-H and 2-H), 4.17 (qd, *J* = 7.2 and 3.0, 2 H, OCH_2), 4.48−4.54 (m, 1 H, 3-H). − ^{19}F NMR (282.2 MHz): δ = −79.67 (d, *J* = 6.1, CF_3). The silylated ethyl ester (30.6 g, 102 mmol) was dissolved in Et_2O (100 mL) and cooled to 0°C. A solution of DIBAH (219 mL, 219 mmol) was slowly added (within 45 min) and the mixture was stirrred at 0°C for 2 h. After completion of the reaction, slow addition of saturated aqueous NH_4Cl (25 mL) and dist. H_2O (25 mL) resulted in the formation of a white jelly-like precipitate. The inhomogeneous mixture was diluted with Et_2O (200 mL), treated with $MgSO_4$ and filtered. The residue was washed with Et_2O (2.0 L) and the combined organic layers were evaporated. Distillation (65°C/0.1 Torr) of the crude product yielded alcohol **3** (19.8 g, 75%) as a colorless oil. − R_f (pentane/Et_2O, 19:1) = 0.15. − $[\alpha]_D^{r.t.}$ = −21.7 (*c* = 1.70, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3621 cm^{-1} (s), 2957 (m), 2931 (m), 2859 (m), 1472 (m), 1390 (m), 1280 (m), 1259 (m), 1168 (s), 1136 (s), 1056 (m), 939 (w), 910 (w), 885 (w), 841 (s). − ^1H NMR (400 MHz): δ = 0.13 (s, 6 H, Me_2Si), 0.91 (s, 9 H, *t*Bu), 1.47 (t, *J* = 5.0, 1 H, OH), 1.78−1.86 (m, 1 H, 2-H), 1.90−1.98 (m, 1 H, 2-H), 3.77−3.85 (m, 2 H, 1-H), 4.16−4.24 (m, 1 H, 3-H). − ^{13}C NMR (100 MHz): δ = 125.23 (q, $J_{(C,F)}$ = 282.6, CF_3), 68.21 (qd), 57.98 (t), 33.42 (t), 25.61 (q), 18.09 (s), −5.07 (q), −5.12 (q). − ^{19}F NMR (282.2 MHz): δ = −78.87 (d, *J* = 6.5). − MS; *m*/*z* (%): 259 (3) [(M + 1)$^+$], 241 (1), 221 (1), 201 (100), 173 (9), 153 (21), 133 (8), 115 (4), 107 (16), 97 (6), 85 (21), 77 (97), 75 (92), 57 (47), 41 (10), 29 (11).

(*S*)-*tert*-Butyl[3-iodo-1-(trifluoromethyl)propoxy]dimethylsilane (4): According to the general literature procedure,[34] triphenylphosphane (33.8 g, 129 mmol), imidazole (8.80 g, 129 mmol) and iodine (32.8 g, 129 mmol) were dissolved in CH_2Cl_2 (420 mL) and the resulting mixture was treated with alcohol **3** (16.7 g, 64.6 mmol) and stirred for 2.5 h at r.t. Evaporation of the solvent and

purification by FC (pentane) yielded the colorless, liquid product **4** (20.7 g, 87%). – R_f (pentane) = 0.62. – $[\alpha]_{589}^{r.t.}$ = −44.0 (*c* = 1.95, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 2956 cm^{-1} (m), 2931 (m), 2859 (m), 1472 (w), 1390 (w), 1155 (s), 1133 (m), 1069 (w), 937 (m), 875 (m), 839 (s). – ^1H NMR (400 MHz): δ = 0.16 (s, 3 H, MeSi), 0.17 (s, 3 H, MeSi), 0.91 (s, 9 H, *t*Bu), 2.10−2.16 (m, 2 H, 2-H), 3.15−3.22 (m, 1 H, 3-H), 3.31−3.37 (m, 1 H, 3-H), 4.04−4.12 (m, 1 H, 1-H). – ^{13}C NMR (100 MHz): δ = 124.84 (q, $J_{(C,F)}$ = 282.8, CF_3), 71.06 (qd), 34.64 (t), 25.65 (q), 18.15 (s), 0.90 (t), −4.57 (q), −5.10 (q). – ^{19}F NMR (283 MHz): δ = −78.35 (d, *J* = 6.3, CF_3). – MS; *m*/*z* (%): 367 (< 1) [(M − 1)$^+$], 337 (1), 311 (1), 215 (44), 187 (74), 167 (10), 155 (11), 143 (7), 107 (9), 88 (5), 77 (100), 59 (45), 57 (33), 41 (15), 29 (7). – $C_{10}H_{20}F_3IOSi$ (368.25): calcd. C 32.62, H 5.47; found C 32.79, H 5.67.

(*S*)-2-[3-(*tert*-Butyldimethylsiloxy)-4,4,4-trifluorobutyl][1,3]-dithiane-2-carbaldehyde (5): As described in ref.[8] with the nonfluorinated analog of **5**, 1,3-dithiane (3.32 g, 27.6 mmol) in THF (80 mL) was cooled to −10°C and treated with BuLi (18.5 mL, 27.8 mmol) for 2 h at −10°C. The resulting solution was cooled to −100°C, and iodide **4** (10.2 g, 27.8 mmol) was slowly added. The mixture was stirred at −100°C for 1 h, then at −78°C for 6 h and then allowed to warm to r.t. overnight. The clear solution was cooled to −40°C, treated with BuLi (23.1 mL, 34.7 mmol), stirred overnight at −26°C and then cooled to −78°C. DMF (4.3 mL, 55.4 mmol) was quickly added to the heterogeneous mixture, which was stirred for 1 h at −78°C, and then allowed to warm up to −20°C within 30 min. Half saturated aqueous NaCl (200 mL) was added and the layers were separated. The aqueous layer was additionally extracted with pentane (4 × 150 mL) and the combined org. layers were washed with aqueous KOH (7%, 2 × 100 mL), with water (100 mL) and saturated aqueous NaCl (100 mL). Removal of the solvent and drying of the residue under HV yielded a crystalline, slightly orange crude material (10.2 g, 95%) which was recrystallized (2 times from hexane) yielding product **5** (8.17 g, 76%). – R_f (pentane/Et_2O, 7:3) = 0.60. – M.p. 45.8−46.6°C. – $[\alpha]_D^{r.t.}$ = −5.83 (*c* = 1.97, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 2957 cm^{-1} (m), 2932 (m), 2860 (m), 1716 (s), 1472 (w), 1464 (w), 1426 (w), 1364 (w), 1279 (m), 1261 (m), 1170 (s), 1142 (s), 841 (s). – ^1H NMR (400 MHz): δ = 0.11 (s, 6 H, Me_2Si), 0.91 (s, 9 H, *t*Bu), 1.71−2.13 (m, 6 H, 3 CH_2), 2.62 (ddd, *J* = 14.3, 4.3 and 3.2, 2 H, 4-H and 6-H), 3.03 (ddd, *J* = 14.3, 12.8 and 2.5, 2 H, 4-H and 6-H), 3.01−3.98 (m, 1 H, 3′-H), 9.03 (s, 1 H, CHO). – ^{13}C NMR (75 MHz): δ = 188.92 (d), 124.80 (q, $J_{(C,F)}$ = 282.5, CF_3), 76.80 (qd), 57.56 (s), 30.47 (t), 26.67 (t), 25.63 (q), 25.45 (t), 24.19 (t), 18.10 (s), −4.83 (q), −5.06 (q). – ^{19}F NMR (283 MHz): δ = −78.15 (d, *J* = 6.3, CF_3). – MS; *m*/*z* (%): 387 (< 1) [(M − 1)$^+$], 359 (100), 331 (96), 303 (8), 227 (22), 145 (21), 119 (15), 107 (12), 77 (23), 73 (27), 57 (6), 41 (7). – $C_{15}H_{27}F_3O_2S_2Si$ (388.5): calcd. C 46.36, H 7.00; found C 46.82, H 6.95.

Methyl (*E*,*S*)-3-{2-[3-(*tert*-Butyldimethylsiloxy)-4,4,4-trifluorobutyl][1,3]dithian-2-yl}acrylate (6): A solution of aldehyde **5** (5.10 g, 13.1 mmol) and methyl (triphenylphosphoranylidene)acetate (7.03 g, 21.0 mmol) in toluene (60 mL) was stirred at 90°C overnight. After removal of the solvent, the residue was dissolved in CH_2Cl_2 and purified by FC (pentane/Et_2O, 19:1) yielding methyl ester **6** (5.54 g, 95%) as a colorless oil which crystallized upon standing at −20°C. – R_f (pentane/Et_2O, 7:3) = 0.43. – M.p. 43.8−44.8°C. – $[\alpha]_D^{r.t.}$ = +3.26 (*c* = 1.09, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 2953 cm^{-1} (m), 2859 (m), 1726 (s), 1646 (m), 1473 (w), 1435 (m), 1363 (w), 1278 (s), 1166 (s), 1140 (s), 1042 (w), 982 (w), 840 (s), 780 (m). – ^1H NMR (400 MHz): δ = 0.10 (s, 6 H, Me_2Si), 0.91 (s, 9 H, *t*Bu), 1.74−1.94 (m, 4 H, 2 CH_2), 2.01−2.09 (m, 2 H, CH_2), 2.68 (dt, *J* = 14.3 and 4.5, 2 H, 4′-H and 6′-H), 2.87 (ddd, *J* = 14.4, 11.6 and 2.8, 2 H, 4′-H and 6′-H), 3.78 (s, 3 H, OCH_3), 3.87−3.96 (m, 1 H, 3″-H), 6.19 (d, *J* = 15.5, 1 H, 2-H), 6.88 (d, *J* = 15.5, 1 H, 3-H). – ^{13}C NMR (100 MHz): δ = 166.59 (s), 149.74 (d), 124.87 (q, $J_{(C,F)}$ = 282.8, CF_3), 123.49 (d), 70.68 (dq), 53.09 (s), 51.80 (q), 36.24 (t), 27.07 (t), 25.63 (q), 25.42 (t), 24.83 (t), 18.10 (s), −4.80 (q), −5.06 (q). – ^{19}F NMR (283 MHz): δ = −78.22 (d, *J* = 6.5, CF_3). – MS; *m*/*z* (%): 444 (3.5) [M$^+$], 429 (2), 413 (7), 387 (100), 355 (13), 338 (18), 313 (5), 281 (32), 269 (7), 229 (7), 203 (30), 171 (25), 154 (21), 143 (7), 125 (28), 111 (44), 77 (46), 73 (71), 59 (19), 57 (17), 41 (19).

(*E*,*S*)-3-{2-[3-(*tert*-Butyldimethylsiloxy)-4,4,4-trifluorobutyl]-[1,3]dithian-2-yl}acrylic Acid (7): An aqueous solution of LiOH (1.0 N, 100 mL) was added to a solution of ester **6** (6.38 g, 15.35 mmol) in THF (170 mL) which was vigorously stirred at r.t. for 10 h. The inhomogeneous mixture was cooled in an ice bath, acidified with HCl (1 N) to pH = 1−2 and saturated with NaCl. The aqueous layer was extracted with Et_2O (5 × 100 mL), then the combined organic layers were dried ($MgSO_4$) and the solvent was removed. Drying (HV) yielded the desired acid **7** quantitatively, containing traces of THF which had no determinable effects for the subsequent reaction. Pure acid **7** was obtained by purification by FC (Et_2O). – R_f (pentane/Et_2O, 3:1) = 0.09. – $[\alpha]_D^{r.t.}$ = +2.6 (*c* = 1.30, $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3000 cm^{-1} (w, br.), 2957 (m), 2951 (m), 2859 (m), 1699 (s), 1644 (m), 1472 (w), 1415 (w), 1364 (w), 1280 (m), 1169 (s), 1142 (s), 1042 (w), 983 (w), 841 (m). – ^1H NMR (500 MHz): δ = 0, period10 (s, 3 H, MeSi), 0.11 (s, 3 H, MeSi), 0.91 (s, 9 H, *t*Bu), 1.75−1.97 (m, 4 H, 2 CH_2), 2.02−2.12 (m, 2 H, CH_2), 2.69 (d,[35] *J* = 5.0, 2 H, 4′-H and 6′-H), 2.88 (ddd,[36] *J* = 11.7, 1.7, 4′-H and 6′-H), 3.89−3.96 (m, 3″-H), 6.20 (d, *J* = 15.4, 2-H), 7.00 (d, *J* = 15.4, 3-H). – ^{13}C NMR (100 MHz): δ = 170.76 (s), 152.10 (d), 124.83 (q, $J_{(C,F)}$ = 282.9, CF_3), 122.76 (d), 70.65 (qd, $J_{(C,F)}$ = 31.1), 52.96 (s), 36.13 (t), 27.07 (t), 25.61 (q), 25.45 (t), 24.73 (t), 10.08 (s), −4.83 (q), −5.08 (q). – ^{19}F NMR: δ = −77.47 (d, $J_{(C,F)}$ = 6.4, CF_3). – EI MS; *m*/*z* (%): 430 (4) [M$^+$], 413 (< 1), 387 (26), 373 (100), 355 (51), 316 (6), 299 (10), 281 (19), 265 (47), 239 (25), 217 (8), 205 (22), 203 (17), 189 (48), 171 (42), 125 (30), 107 (54).

Methyl (*E*,*S*)-3-[2-(4,4,4-Trifluoro-3-hydroxybutyl)[1,3]dithian-2-yl]-acrylate (8): In a 1-L polyethylene flask, a solution of silyl ether **6** (4.78 g, 10.75 mmol) in THF (200 mL) was cooled to 0°C and treated with HF in pyridine (12 mL, ca. 460 mmol). The mixture was then stirred for 1 h at 0°C, then at r.t. for 65 h. The solution was diluted with Et_2O (400 mL), cooled to 0°C and neutralized with saturated aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous NaCl (2 × 100 mL), then dried ($MgSO_4$) and the solvent was removed by RV and the residue dried under HV. Purification by FC (pentane/Et_2O, 3:1) yielded ester **8** (3.27 g, 92%) as a colorless oil. – R_f (pentane/Et_2O, 3:1) = 0.15. – $[\alpha]_D^{r.t.}$ = −14.6 (*c* = 0.96, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 3444 cm^{-1} (br., s), 2952 (m), 2909 (m), 1705 (s), 1645 (m), 1437 (m), 1277 (s), 1168 (s), 1137 (s), 1039 (w), 981 (w), 738 (m), 696 (m). – ^1H NMR (400 MHz): δ = 1.70−1.97 (m, 4 H, 2 CH_2), 2.03−2.11 (m, 1 H), 2.15−2.22 (m, 1 H), 2.24 (d, *J* = 6.2, 1 H, OH), 2.70 (ddd, *J* = 14.5, 4.7 and 3.3, 2 H, 4′-H and 6′-H), 2.88 (ddd, *J* = 14.5, 11.8 and 2.7, 2 H, 4′-H and 6′-H), 3.79 (s, 3 H, OCH_3), 3.81−3.96 (m, 1 H, 3′′-H), 6.21 (d, *J* = 15.5, 1 H, 2-H), 6.90 (d, *J* = 15.5, 1 H, 3-H). – ^{13}C NMR (100 MHz): δ = 166.66 (s), 149.63 (d), 124.85 (q, $J_{(C,F)}$ = 282.1, CF_3), 123.54 (d), 77.3 (dq), 52.97 (s), 51.87 (q), 36.65 (t), 27.08 (t), 27.06 (t), 24.77 (t), 24.22 (t). – ^{19}F NMR (283 MHz): δ = −80.27 (d, *J* = 5.9, CF_3). – MS; *m*/*z* (%): 330 (12) [M$^+$], 299 (5), 271 (5), 245 (< 1), 237 (2), 224 (100), 203 (15), 191 (6), 144 (3), 125 (5), 111 (66), 84 (8), 74 (18), 59 (10), 41 (18).

− $C_{12}H_{17}O_2F_3S_2$ (330.4): calcd. C 43.63, H 5.19; found C 43.80, H 5.50.

(*E*,*S*)-3-[2-(4,4,4-Trifluoro-3-hydroxybutyl)[1,3]dithian-2-yl]-acrylic Acid (9): In a 250-mL polyethylene flask, a solution of the crude silyl ether **7** (7.04 g) in THF (50 mL) was prepared and cooled in an ice bath. HF in pyridine (9:1, 10 mL) was added and the mixture was stirred at 0°C for 15 min and at r.t. for 90 h. The solution was diluted with CH_2Cl_2 (100 mL), then washed with water (4 × 50 mL) and the org. layer was dried ($MgSO_4$). Most of the solvent was removed by RV and under HV, whereas the amount of remaining THF could be reduced to ca. 5% by azeotropic distillation with Et_2O, resulting in the "monomer" **9** (4.54 g,[37] 93% from **6**). This material was used in the macrolactonization step without any further purification. − R_f (Et_2O) = 0.25. − $[\alpha]_D^{r.t.}$ = −15.9 (*c* = 0.99, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3597 cm^{-1} (w), 3349 (br., m), 2907 (m), 1699 (s), 1645 (m), 1425 (m), 1278 (s), 1170 (s), 1139 (s), 1041 (w), 983 (w). − ^{1}H NMR (500 MHz): δ = 1.72−1.80 (m, 1 H, 2″-H), 1.82−1.99 (m, 3 H, 1″-H, 2″-H and 5′-H), 2.08 (d, br, *J* = 11.0, 1 H, 5′-H), 2.20 (td, *J* = 12.8 and 3.2, 1 H, 1″-H), 2.71 (ddd, *J* = 11.7, 6.3 and 4.3, 2 H, 4′-H and 6′-H), 2.88 (ddd, *J* = 14.5, 11.7 and 2.5, 2 H, 4′-H and 6′-H), 3.88−3.95 (m, 1 H, 3″-H), 6.22 (d, *J* = 15.4, 1 H, 2-H), 7.01 (d, *J* = 15.4, 1 H, 3-H). − ^{13}C NMR (100 MHz): δ = 171.00 (s), 152.02 (d), 124.85 (q, $J_{(C,F)}$ = 282.0, CF_3), 122.83 (d), 70.30 (dq), 52.84 (s), 36.54 (t), 27.10 (t), 27.06 (t), 24.68 (t), 24.23 (t). − ^{19}F NMR (283 MHz): δ = −80.32 (d, $J_{(H,F)}$ = 6.3, CF_3). − MS; *m*/*z* (%): 316 (15) [M^+], 271 (4), 229 (8), 210 (36), 189 (37), 165 (4), 145 (6), 130 (17), 115 (17), 107 (45), 106 (72), 97 (82), 87 (12), 74 (100), 55 (18), 41 (50).

(7*E*,11*S*,20*E*,24*S*)-11,24-Bis(trifluoromethyl)-10,23-dioxa-1,5,15,19-tetrathiadispiro[5.7.5.7]hexacosa-7,20-diene-9,22-dione (10a): According to the general esterification procedure described in the literature,[38] 1-chloro-1-(dimethylamino)-2-methyl-1-propene (0.340 mL, 2.52 mmol) was added dropwise within 10 min to a solution of the crude hydroxy acid **9** (759 mg, 2.29 mmol) in CH_2Cl_2 (15 mL) at r.t. The clear reaction mixture was stirred for 10 min[39] at ambient temperature, then diluted with toluene (15 mL) and the remaining solution was added dropwise within 4 h (syringe pump) to a refluxing solution of DMAP (2.79 g, 22.9 mmol) in toluene (250 mL). The end of the needle was immersed into the condensation front of the solution in a Vigreux column (30 cm) to avoid drop formation. The pressure was equalized through an additional coiled condenser allowing a stable condensation front in the Vigreux column. The mixture was heated under reflux for another 4 h and the solvent was removed by RV. The crude product was stored overnight at −20°C[40] and then separated by FC (pentane/Et_2O, 4:1) from larger macrocycles yielding diolide **10a** (74.9 mg, 11%) and impure triolide **10b** (22.0 mg, 3%). The triolide **10b** was purified as described below. The diolide was then dissolved in CH_2Cl_2 (1.6 mL) and treated with hexane (4.0 mL). Removal of CH_2Cl_2 by RV resulted in the precipitation of **10a**. Removal of the mother liquor and drying of the precipitate (HV) yielded pure diolide **10a** (64.3 mg, 9%). − R_f (pentane/Et_2O, 3:1) = 0.29. − M.p. 176.0−176.3°C. − $[\alpha]_D^{r.t.}$ = −81.7 (*c* = 0.920, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2911 cm^{-1} (w), 1734 (s), 1637 (m), 1446 (w), 1425 (w), 1403 (w), 1264 (m), 1146 (s), 1110 (m), 1036 (w), 983 (w), 908 (w). − ^{1}H NMR (400 MHz): δ = 1.60−1.77 (m, 2 H, 2 *H*−C−H), 1.84−1.94 (*m*, 2 H, 2 H−C−*H*), 2.06−2.24 (m, 8 H, 4 CH_2), 2.67−2.74 (m, 4 H, 2-H, 4-H, 16-H, 18-H), 2.79−2.87 (ddt, *J* = 14.5, 11.8 and 2.8, 4 H, 2-H, 4-H, 16-H, 18-H), 5.42 (m, 2 H, 11-H and 24-H), 6.24 (d, *J* = 15.5, 2 H, 8-H, 21-H), 6.92 (d, *J* = 15.5, 2 H, 7-H and 20-H). − ^{13}C NMR (100 MHz): 163.19 (s), 152.17 (d), 124.30 (q, $J_{(C,F)}$ = 281.3, CF_3), 123.28 (d), 68.27 (qd, $J_{(C,F)}$ = 32.8), 52.83 (s), 34.40 (t), 27.46 (t), 26.80 (t), 24.76 (t), 22.32 (t). − ^{19}F NMR: δ = −74.56 (*d*, $J_{(H,F)}$ = 7.5, CF_3). − EI MS; *m*/*z* (%): 596 (7) [M^+], 490 (< 1), 254 (< 1), 220 (3), 207 (15), 205 (13), 192 (12), 149 (6), 106 (49). − MALDI MS; *m*/*z*: 597 [M^+], 619 [(M + Na)$^+$]. − $C_{22}H_{26}F_6O_4S_4$ (596.7): calcd. C 44.28, H 4.39; found C 44.16, H 4.45. − The ^{1}H-NMR and ^{13}C-NMR spectra correspond with small differences in the chemical shifts (low-field shifts caused by fluorine substituents) with those of the nonfluorinated analog.

Triolide 10b: The triolide-containing fractions received during the purification of crude diolide **10a** were collected, resulting in 130 mg of the soiled triolide **10b**. Purification by FC (2 ×; pentane/Et_2O, 4:1) and recrystallization (3 × from CH_2Cl_2/hexane, as described for the diolide) yielded the analytically pure triolide **10b** (45.5 mg). − R_f (pentane/Et_2O, 3:1) = 0.24. − M.p. 197−198°C. − $[\alpha]_D^{r.t.}$ = +13.09 (*c* = 0.59, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2916 cm^{-1} (w), 1737 (s), 1641 (m), 1448 (w), 1425 (w), 1399 (w), 1364 (w), 1300 (m), 1280 (s), 1264 (s), 1146 (s), 1074 (m), 981 (m), 908 (m). − ^{1}H NMR (400 MHz): δ = 1.73−1.91 (m, 9 H, 3 CH_2 and 3 *H*−C−H), 2.00−2.11 {m, 6 H, 3 H−C−H, 3 *H*−C[C(S)]−H}, 2.24−2.32 {m, 3 H, 3 H−C[C(S)]−*H*}, 2.67−2.74 [m, 6 H, 6 *H*−C(S)−H], 2.80−2.95 [m, 6 H, 6 H−C(S)−*H*], 5.35−5.43 [m, 3 H, H−C(CF_3)], 6.23 (d, *J* = 15.4, 3 H, α-H), 6.96 (d, *J* = 15.4, β-H). − ^{13}C NMR (100 MHz): δ = 164.53 (s), 153.12 (d), 123.52 (q, $J_{(C,F)}$ = 281.2, CF_3), 121.17 (d), 69.58 [qd, $J_{(C,F)}$ = 32.6, C(CF_3)], 53.28 (s), 35.97 (t), 27.03 (t), 24.12 (t), 22.93 (t). − ^{19}F NMR: δ = −76.51 (d, $J_{(H,F)}$ = 6.4, CF_3). − MALDI MS (CH_2Cl_2, without a matrix); *m*/*z*: 917.8 [(M + Na)$^+$]. − NH_4-DCI MS; *m*/*z* (%): 918 (< 1) [(M + 24)$^+$], 917 (2) [(M + 23)$^+$], 916 (6) [(M + 22)$^+$], 915 (14) [(M + 21)$^+$], 914 (39) [(M + 20)$^+$], 913 (40) [(M + 19)$^+$], 912 (100) [(M + 18)$^+$], 895 (9) [(M + 1)$^+$], 894 (16) [M^+]. − $C_{33}H_{39}O_6F_9S_6$ (895.05): calcd. C 44.28, H 4.39; found C 44.09, H 4.55.

(*S*,*S*)-(−)-8′,8′,8′,16′,16′,16′-Hexafluoropyrenophorin [8,16-Bis(trifluoromethyl)-1,9-dioxacyclohexadeca-3,11-diene-2,5,10,13-tetraone (1d)] from 10a: According to the general procedure of Fujita et al.,[15] a solution of $Hg(ClO_4)_2 \cdot 3\,H_2O$ (0.672 g, 1.48 mmol) in THF (7 mL) was added at r.t. to a solution of the dithiane-protected diolide **10a** (0.210 g, 0.352 mmol) in THF (7 mL), resulting in the precipitation of a white solid after a few seconds. The mixture was stirred for 5 min and poured into a NaH_2PO_4/Na_2HPO_4 buffer solution (pH = 6, 100 mL). Extraction with $CHCl_3$ (5 × 300 mL), drying ($MgSO_4$) and removal of the solvent by RV and HV resulted in the crude product **1d** (0.134 g) as tiny sheets. The thiol-like smelling product was suspended in CH_2Cl_2 (5 mL) and treated with hexane (5 mL). The CH_2Cl_2 was evaporated by RV and the remaining mother liquor was removed by decantation. The purification was repeated and the residue was sublimated (160−200°C/10^{-5} bar). Subsequent trituration with from CH_2Cl_2/hexane (2 ×, see above), yielded the analytically pure hexafluoropyrenophorin (**1d**, 69.2 mg, 47%). − R_f (pentane/Et_2O, 1:1) = 0.26. − M.p. 262−266°C. − $[\alpha]_D^{r.t.}$ = −26.8 [*c* = 0.175, $CF_3CH(OH)CF_3$/CH_2Cl_2 1.5:1]. − IR (KBr): $\tilde{\nu}$ = 3068 cm^{-1} (m), 2950 (w), 1737 (s), 1698 (s), 1635 (m), 1439 (m), 1391 (m), 1354 (m), 1320 (w), 1271 (s), 1232 (w), 1190 (s), 1159 (s), 1140 (s), 1103 (m), 1081 (m), 1050 (m), 999 (m), 923 (w), 880 (w), 742 (w), 691 (w). − ^{1}H NMR (300 MHz): δ = 2.20−2.30 (m, 2 H, 7-H, 15-H), 2.46−2.76 (m, 6 H, 2 CH_2, 7-H, 15-H), 5.36−5.49 (m, 2 H, 8-H, 16-H), 6.57 (d, *J* = 15.8, 2 H, 3-H, 11-H), 7.02 (d, *J* = 15.8, 2 H, 4-H, 12-H).[41] − ^{19}F NMR: δ = −76.78 (d, $J_{(H,F)}$ = 6.4, CF_3). − NH_4-DCI MS; *m*/*z* (%): 438 (60) [(M + 22)$^+$],[42] 437 (18) [(M + 21)$^+$], 436 (100) [(M + 20)$^+$], 435 (6) [(M + 19)$^+$], 434 (29) [(M + 18)$^+$], 230 (5) [(M/2 + 22)$^+$], 228 (20) [(M/2 + 20)$^+$], 226 (4) [(M/

2 + 18)$^+$]. − $C_{16}H_{14}F_6O_6$ (416.27): calcd. C 46.17, H 3.39; found C 45.98, H 3.40.

8,16,24-Tris(trifluoromethyl)-1,9,17-trioxacyclotetracosa-3,11,19-triene-2,5,10,13,18,21-hexaone (11): According to the general procedure of Fujita et al.,[15] a solution of $Hg(ClO_4)_2 \cdot 3\,H_2O$ (0.100 g, 0.220 mmol) in THF (1 mL) was added at r.t. to a solution of the dithiane-protected triolide **10b** (0.0293 g, 0.0327 mmol) in THF (1 mL). The mixture was stirred for 5 min and the clear, slightly yellowish solution was poured into a NaH_2PO_4/Na_2HPO_4 buffer solution (pH = 6, 10 mL). Extraction with $CHCl_3$ (3 × 30 mL), drying ($MgSO_4$) and removal of the solvent by RV and HV afforded crude product **11** (22.9 mg) as a white solid. Purification by FC (Et_2O/pentane, 1:1 to Et_2O/CH_2Cl_2, 9:1) resulted in a slightly impure product (19.2 mg) which was recrystallized twice from CH_2Cl_2/hexane as follows: The powdery solid was dissolved in CH_2Cl_2 (2 mL) and treated with hexane (1 mL) resulting in the precipitition of the triolide. The CH_2Cl_2 was evaporated by RV and the remaining mother liquor was removed by decantation. Drying under HV yielded the analytically pure triolide **11** (16.5 mg, 81%). − R_f (pentane/Et_2O, 1:1) = 0.18. − M.p. 143.6−144.0°C. − $[\alpha]_D^{r.t.}$ = +4.90 (c = 0.102, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3067 cm^{-1} (w), 2954 (w), 1735 (s), 1702 (s), 1639 (w), 1445 (w), 1396 (w), 1346 (w), 1294 (s), 1270 (s), 1174 (s), 1098 (m), 1054 (m), 984 (m), 884 (w), 763 (w), 703 (w). − ^{1}H NMR (400 MHz): δ = 2.14−2.22 (m, 3 H, 7-H, 15-H, 23-H), 2.29−2.36 (m, 3 H, 7-H, 15-H, 23-H), 2.66−2.87 (m, 6 H, 6-H, 14-H and 22-H), 5.46−5.53 (m, 3 H, 8-H, 16-H, 24-H), 6.65 (d, J = 16.1, 3 H, 3-H, 11-H, 19-H), 7.09 (d, J = 16.1, 3 H, 4-H, 12-H, 20-H). − ^{13}C NMR (100 MHz): δ = 196.12 (s), 163.55 (s), 140.93 (d), 128.89 (d), 123.29 (q, $J_{(C,F)}$ = 280.7, CF_3), 69.38 (qd, $J_{(C,F)}$ = 33.0, C−CF_3), 35.48 (t), 20.89 (t). − ^{19}F NMR: δ = −76.48 (d, $J_{(H,F)}$ = 6.3, CF_3). − NH_4-DCI MS; m/z (%): 648 (12) [(M + 24)$^+$], 647 (4) [(M + 23)$^+$], 646 (17) [(M + 22)$^+$], 645 (10) [(M + 21)$^+$], 644 (38) [(M + 20)$^+$], 643 (23) [(M + 19)$^+$], 642 (81) [(M + 18)$^+$], 228 (100) [(M/3 + 20)$^+$]. − $C_{24}H_{21}F_9O_9$ (624.41): calcd. C 46.17, H 3.39; found C 45.94, H 3.66.

(*S*)-3-Hydroxy-2-(trifluoromethyl)propionic Acid (12) and (*R*)-3-Hydroxy-2-(trifluoromethyl)propionic Acid (*ent*-12): The enantiomerically pure acids **12** and *ent*-**12** were prepared according to the procedure described in ref.[5] with overall yields of 55%.

(2*R*,5*S*)- and (2*S*,5*S*)-2-*tert*-Butyl-5-(trifluoromethyl)[1,3]dioxan-4-one (13b and 13d): A mixture of trifluoro-*Roche* acid **12** (1.07 g, 6.77 mmol), pivalaldehyde (2.45 mL, 22.1 mmol) and Dowex 50 W (ca. 0.3 g) in CH_2Cl_2 (35 mL) was refluxed overnight using a Dean−Stark apparatus. After cooling to r.t., the suspension was diluted with CH_2Cl_2 (30 mL), filtered and washed with saturated aqueous $NaHCO_3$ (3 × 25 mL). The organic layer was dried ($MgSO_4$) and concentrated by RV and HV. Recrystallization from pentane yielded a mixture of **13b** and **13d** (1.3:1, 0.707 g, 46%) which was separated by HPLC (Chiraspher®, hexane/*i*PrOH, 99:1). − (2*R*,5*S*)-**13b**: R_f (pentane/Et_2O, 2:1) = 0.25. − t_R (Chiracel OD®; hexane/*i*PrOH, 99:1) = 22.4 min. − M.p. 81.8−82.1°C. − $[\alpha]_D^{r.t.}$ = −19.0 (c = 1.09, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2965 cm^{-1} (m), 1735 (s), 1484 (m), 1407 (m), 1377 (m), 1269 (s), 1140 (s), 1030 (w), 980 (m). − ^{1}H NMR (400 MHz): δ = 0.99 (s, 9 H, *t*Bu), 3.32 (qdd, J = 8.9, 6.1 and 2.5, 1 H, 5-H), 4.08 (ddq, J = 12.4, 6.1 and 1.4, 1 H, 6-H), 4.49 (dd, J = 12.4 and 2.5, 1 H, 6-H), 4.94 (s, 1 H, 2-H). − ^{13}C NMR (100 MHz): δ = 160.96 (s), 123.57 (q, $J_{(C,F)}$ = 280.8, CF_3), 109.87 (d), 62.78 (t), 44.95 (qd), 35.34 (s), 23.67 (q). − ^{19}F NMR (283 MHz): δ = −67.22 (d, $J_{(H,F)}$ = 6.3, CF_3). − MS; m/z (%): 227 (1) [(M + 1)$^+$], 169 (16), 141 (13), 123 (62), 86 (14), 71 (11), 57 (100), 43 (19), 41 (26), 29 (18). − $C_9H_{13}F_3O_3$ (226.20): calcd. C 47.79, H 5.79; found C 47.90, H 5.85. − The relative configuration was assigned by NOE.[1] − **(2*S*,5*S*)-13d:** − R_f (pentane/Et_2O, 2:1) = 0.25. − t_R (Chiracel OD®; hexane/*i*PrOH, 99:1) = 9.6 min. − M.p. 70.6−71.0°C. − $[\alpha]_D^{r.t.}$ = +28.1 (c = 1.07, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2965 cm^{-1} (m), 1755 (s), 1483 (w), 1395 (m), 1332 (m), 1274 (m), 1131 (s), 1052 (m), 1029 (m), 974 (m), 895 (m). − ^{1}H NMR (400 MHz): δ = 0.99 (s, 9 H, *t*Bu) 3.57 (dqd, J = 11.1, 8.8 and 8.1, 1 H, 5-H), 3.96 (t, J = 11.6, 1 H, 6-H), 4.48 (dd, J = 11.6 and 8.1, 1 H, 6-H), 4.95 (s, 1 H, 2-H). − ^{13}C NMR (100 MHz): δ = 160.90 (s), 123.08 (q, $J_{(C,F)}$ = 279.4, CF_3), 110.18 (d), 63.32 (t), 45.06 (dq), 35.33 (s), 23.68 (q). − ^{19}F NMR (283 MHz): δ = −66.86 (d, $J_{(H,F)}$ = 9.2, CF_3). − MS; m/z (%): 227 (< 1) [(M + 1)$^+$], 169 (7), 141 (8), 123 (40), 96 (5), 91 (10), 86 (16), 77 (16), 71 (8), 69 (6), 57 (100), 43 (23), 41 (47), 29 (28), 27 (20). − $C_9H_{13}O_3F_3$ (226.20): calcd. C 47.79, H 5.79; found C 47.88, H 5.90. − The relative configuration was confirmed by NOE.[1]

(2*R*,5*R*)- and (2*S*,5*R*)-2-*tert*-Butyl-5-(trifluoromethyl)[1,3]dioxan-4-one (13a and 13c): By analogy with the preparation of **13b** and **13d** (see above), acid *ent*-**12** was converted into the corresponding compounds **13a** and **13c**. − **(2*R*,5*R*)-13a:** − R_f (pentane/Et_2O, 2:1) = 0.25. − t_R (Chiracel OD®; hexane/*i*PrOH, 99:1) = 7.5 min. − M.p. 70.6−71.0°C. − $[\alpha]_D^{r.t.}$ = −27.6 (c = 1.10, $CHCl_3$). − The ^{1}H-NMR spectrum corresponds to that of (2*S*,5*S*)-**13d**. − **(2*S*,5*R*)-13c:** − R_f (pentane/Et_2O, 2:1) = 0.25. − t_R (Chiracel OD®; hexane/*i*PrOH, 99:1) = 17.3 min. − M.p. 81.6−82.0°C. − $[\alpha]_D^{r.t.}$ = +19.7 (c = 1.17, $CHCl_3$). − The ^{1}H-NMR spectrum corresponds to that of (2*R*,5*S*)-**13b.**

***cis*-2-*tert*-Butyl-*N*,*N*-diisopropyl-4-oxo[1,3]dioxane-5-carboxamide (*rac*-*cis*-14 and *rac*-*trans*-14):** A solution of the dioxanones **13a** and **13b** (0.501 g, 2.21 mmol) in THF (20 mL) was cooled to −105°C and treated with a solution of LDA (3.1 mL, 2.21 mmol, in THF/hexane) and stirred for 30 min. The solution was then treated with MeI (0.2 mL, 3.21 mmol) and allowed to cool to r.t. overnight. Saturated aqueous $NaHCO_3$ (30 mL) was added and the aqueous layer was extracted with Et_2O (3 × 30 mL). Drying of the combined organic layers ($MgSO_4$), evaporation of the solvent and purification of the residue by FC (pentane/Et_2O, 4:1) yielded the non-fluorinated *cis* product *rac*-*cis*-**14** (0.181 g, 29%) and *trans* epimer (first eluted isomer) *rac*-*trans*-**14** (0.086 g, 15%). − ***rac*-*cis*-14:** − R_f (pentane/Et_2O, 2:1) = 0.18. − M.p. 130.4−130.8°C. − IR ($CHCl_3$): $\tilde{\nu}$ = 2975 cm^{-1} (m), 1746 (s), 1645 (s), 1445 (m), 1406 (w), 1371 (m), 1338 (m), 1282 (m), 1157 (w), 1133 (w), 981 (m). − ^{1}H NMR (400 MHz): δ = 0.99 (s, 9 H, *t*Bu), 1.20 (d, J = 6.7, 3 H, Me), 1.29 (d, J = 6.5, 3 H, Me), 1.39 (d, J = 6.9, 3 H, Me), 1.42 (d, J = 6.8, 3 H, Me), 3.45−3.57 (s, br., 1 H, H−C−N), 3.88 (dd, J = 8.0, 5.0, 5-H), 3.94 (m, 1 H, H−C−N), 4.13 (dd, J = 10.9 and 8.0, 1 H, 6-H), 4.52 (dd, J = 10.9 and 5.0, 1 H, 6-H), 4.94 (s, 1 H, 2-H). − NOE experiment: irradiation at δ = 4.94 (2-H), NOE observed at δ = 0.99 (*t*Bu), 3.88 (5-H) and 4.13 (6-H); irradiation at δ = 3.88 (5-H), observed NOE at δ = 4.13 (weak, 6-H) and 4.94 (2-H); irradiation at δ = 4.13 (6-H), observed NOE at δ = 3.88 (weak, 5-H), 4.52 (6-H) and 4.94 (2-H). − ^{13}C NMR (100 MHz): δ = 166.12 (s), 164.73 (s), 108.10 (d), 65.43 (t), 46.53 (d), 45.13 (d), 35.13 (s), 23.88 (q, *t*Bu), 20.89 (q), 20.68 (q), 20.45 (q), 20.17 (q). − EI MS; m/z (%): 285 (< 1) [(M + 1)$^+$], 270 (1), 242 (6), 228 (11), 200 (12), 184 (22), 166 (7), 156 (26), 140 (24), 128 (25), 112 (21), 100 (25), 86 (100), 70 (13), 55 (51), 43 (39). − $C_{15}H_{27}NO_4$ (285.38): calcd. C 63.13, H 9.54, N 4.91; found C 63.19, H 9.40, N 4.82. − ***rac*-*trans*-14:** − R_f (pentane/Et_2O, 2:1) = 0.29. − ^{1}H NMR (300 MHz): δ = 0.97 (s, 9 H, *t*Bu), 1.22 (d, J = 6.6, 3 H, CH_3), 1.34 (d, J = 6.6, 3 H, CH_3), 1.36 (d, J = 7.4, 3 H, CH_3), 1.39 (d, J = 7.4, 3 H, CH_3), 3.50−3.68 (m, 1 H, 5-H), 3.96 (dd, J = 9.5, 8.2, 1 H, 6-H),

4.05−4.16 (m, 1 H, H−C−N), 4.25−4.36 (m, 1 H, H−C−N), 4.32 (dd, J = 9.5, 5.5, 1 H, 6-H), 5.07 (s, 1 H, 2-H).

Methyl (*S*)-3-Hydroxy-2-(trifluoromethyl)propionate (15): A solution of acid **12** (16.67 g, 0.105 mol) in Et_2O (200 mL) was treated with an ethereal solution of diazomethane[43] until the resulting solution remained yellow. The solvent was removed under reduced pressure by RV at < 20°C. Bulb-to-bulb distillation of the crude product (35−40°C/0.2 Torr) yielded ester **15** (18.1 g, 99%). − $[\alpha]_D^{r.t.}$ = +15.7 (c = 1.80, $CHCl_3$). − *er* = 99.1:0.9 by GC.[5] − IR ($CHCl_3$): $\tilde{\nu}$ = 3617 cm^{-1} (w), 3392 (w, br.), 2957 (w), 1748 (s), 1439 (m), 1317 (s), 1274 (s), 1123 (s), 1043 (m), 894 (w), 838 (w). − ^{1}H NMR (400 MHz): δ = 2.32 (s, br., 1 H, OH), 3.39 (qdd, J = 8.7, 7.2, 4.6, 2-H), 3.48 (s, 3 H, OCH_3), 4.02−4.14 (m, 2 H, 3-H). − ^{13}C NMR (100 MHz): δ = 167.01 (s), 123.72 (q, $J_{(C,F)}$ = 280.2), 58.52 (t), 53.05 (q), 52.10 (qd, $J_{(C,F)}$ = 26.5). − ^{19}F NMR: δ = −66.44 (d, $J_{(H,F)}$ = 9.2, CF_3). − EI MS; *m*/*z* (%): 173 (< 1) [(M + 1)$^+$], 155 (< 1), 142 (60), 123 (18), 111 (18), 103 (37), 91 (100), 77 (6), 71 (9), 59 (16). − $C_5H_7F_3O_3$ (172.1): calcd. C 34.89, H 4.10; found C 34.80, H 4.28.

Methyl (2*S*,2′*RS*)-3-(Tetrahydropyran-2-yloxy)-2-(trifluoromethyl)-propionate (16): To a solution of ester **15** (18.1 g, 0.105 mol) and 3,4-dihydro-2*H*-pyran (17.0 mL, 0.188 mol) in CH_2Cl_2 (325 mL), pyridinium *p*-toluenesulfonate (0.225 g, 0.896 mmol) was added and the solution was stirred overnight at r.t. and then poured into a phosphate buffer solution (50 mL, pH = 7). Extraction with Et_2O (3 × 50 mL), drying ($MgSO_4$) and purification by FC (pentane/Et_2O, 2:1) resulted in the mixture of the enantiomerically pure diastereoisomers of **16** (24.9 g, 93%) which could not be separated by FC. − R_f (pentane/Et_2O, 2:1) = 0.58. − $[\alpha]_D^{r.t.}$ = +24.2 (c = 1.60, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2950 cm^{-1} (m), 1750 (s), 1454 (w), 1439 (m), 1356 (m), 1320 (m), 1277 (m), 1128 (s), 1064 (m), 1034 (s), 973 (m), 911 (w), 870 (w). − ^{1}H NMR (400 MHz): δ = 1.48−1.81 (m, 6 H, 3 CH_2), 3.42−3.56 (m, 2 H, 2-H and *H*CH−O−), 3.81 (s, 3 H, COOMe), 3.74−3.83 (m, 1 H, HC*H*−O− and 0.5 H, 3-H_A), 3.88 (dd, J = 10.1 and 8.4, 0.5 H, 3-H_A), 4.10 (dd, J = 10.1 and 4.9, 0.5 H, 3-H_B), 4.18 (dd, J = 10.1 and 8.1, 0.5 H, 3-H_B), 4.61−4.66 (m, 1 H, −O−CH−O−). − ^{13}C NMR (100 MHz): δ = 166.57 (s), 123.77 (q, $J_{(C,F)}$ = 271.24, CF_3), 99.41 (d), 98.48 (d), 63.08 (t), 63.05 (t), 62.18 (t), 61.75 (t), 52.81 (q), 52.78 (q), 50.97 (qd), 50.85 (qd), 30.26 (t), 30.17 (t), 25.29 (t), 19.06 (t), 18.78 (t). − ^{19}F NMR: δ = −67.05 (d,[44] CF_3). − EI MS; *m*/*z* (%): 256 (1) [M$^+$], 255 (13) [(M − 1)$^+$], 241 (4), 228 (2), 201 (23), 183 (3), 173 (28), 155 (100), 141 (18), 135 (4), 123 (26), 111 (4), 101 (14), 91 (17), 85 (48), 77 (5). − $C_{10}H_{15}F_3O_4$ (256.22): calcd. C 46.88, H 5.90; found C 46.99, H 5.97.

(2*R*,2′*RS*)-3-(Tetrahydropyran-2-yloxy)-2-(trifluoromethyl)-propan-1-ol (17): In a 1-L flask, a cold solution (−40°C) of **16** (15.9 g, 61.9 mmol) in Et_2O (200 mL) was treated within 45 min with DIBAH (135 mL, 0.135 mol) at −40°C. The mixture was first stirred for 15 min at that temperature, then allowed to warm to 0°C within 15 min and then stirred for 4 h at that temperature. The clear homogeneous solution was quenched with saturated aqueous $NaHCO_3$ (16 mL) and allowed to warm to r.t. Et_2O (200 mL) and water (16 mL) were added. The mixture was stirred for 20 min, treated with $MgSO_4$, filtered and concentrated by RV. The residue was purified by bulb-to-bulb distillation (ca. 110°C/0.1 Torr) resulting in the colorless product **17** (12.68 g, 90%). Additional purification[45] by FC (Et_2O/pentane/Et_3N, 7:3:0.1) yielded a mixture of the enantiomerically pure diastereoisomers of **17** (11.8 g, 84%). − R_f (pentane/Et_2O, 2:1) = 0.13; (Et_2O/pentane/Et_3N, 7:3:0.1) = 0.4. − IR ($CHCl_3$): $\tilde{\nu}$ = 3456 cm^{-1} (w, br.), 2949 (m), 1455 (w), 1442 (w), 1385 (m), 1347 (m), 1129 (s), 1076 (m), 1032 (s), 988 (m), 902 (m), 869 (w). − ^{1}H NMR (400 MHz): δ = 1.50−1.62 (m, 4 H, 2 CH_2), 1.70−1.83 (m, 2 H, CH_2), 2.53−2.66 (m, 2 H, 2-H and OH), 3.51−3.58 (m, 1 H, 6′-H), 3.71−3.80 (m, 1 H, 3-H), 3.85−4.12 (m, 4 H, 2 1-H, 3-H and 6′-H), 4.58−4.62 (m, 1 H, 2′-H). − ^{13}C NMR (100 MHz): δ = 126.34 (q, $J_{(C,F)}$ = 280.4, CF_3), 99.98 (d), 99.48 (d), 63.17 (t), 62.97 (t), 58.84 (t), 58.60 (t), 45.95 (qd), 45.71 (qd), 30.49 (t), 30.45 (t), 25.16 (t), 19.77 (t), 19.65 (t). − ^{19}F NMR: δ = −67.79 (2d,[44] CF_3). − EI MS; *m*/*z* (%): 227 (12) [(M − 1)$^+$], 173 (12), 155 (49), 145 (19), 127 (32), 101 (16), 93 (7), 85 (100), 77 (30), 67 (10), 56 (48). − $C_9H_{15}O_3F_3$ (228.21): calcd. C 47.37, H 6.62; found C 47.57, H 6.78.

Determination of the Enantiomeric Purity of 17: A solution of the (*R*)-alcohol **17** (0.116 g, 0.452 mmol) in THF (2.0 mL) was treated with NaH (25 mg, 0.57 mmol), stirred for 15 min, then treated with benzyl bromide (0.070 mL, 0.99 mmol) and stirred overnight at r.t. The mixture was quenched with saturated aqueous $NaHCO_3$ (1.0 mL) and the aqueous layer was removed (pipette). The organic layer was dried ($MgSO_4$), filtered (cotton), concentrated (RV) and shortly dried (HV). The residue was resolved in MeOH (2.0 mL) and treated with DOWEX 50 W (tip of a spatula), stirred for 4 h and filtered. The filtrate was concentrated by RV, shortly dried (HV) and diluted with hexane resulting in a 0.1% solution which was directly used for HPLC analysis (Chiracel OD®; hexane/*i*PrOH, 98:2) showing that no racemization occurred during functional-group manipulations (**12** → **17**). − R_f (pentane/Et_2O, 2:1) = 0.20. − t_R[(*S*)-benzyl ether; Chiracel OD®; hexane/*i*PrOH, 98:2] = 39.3 min, {t_R(*rac*-benzyl ether) = 35.9 and 39.0 min, t_R[(*R*)-benzyl ether] = 36.0}.

(2*RS*,2′*R*)-2-[3-Iodo-2-(trifluoromethyl)propoxy]tetrahydropyran (18): By analogy to the general procedure,[34] triphenylphosphane (15.05 g, 57.4 mmol) and imidazole (7.86 g, 115.9 mmol) were dissolved in CH_2Cl_2 (150 mL) and the resulting clear solution was treated with iodine (13.65 g, 53.8 mmol). A solution of alcohol **17** (9.96 g, 44.1 mmol) in CH_2Cl_2 (35 mL) was added and the mixture was stirred for 10 h at r.t. The solvent was removed (RV) and the residue purified by FC (pentane/Et_2O, 9:1) yielding pure iodide **18** (12.26 g, 83%) as a colorless oil. − R_f (pentane/Et_2O, 2:1) = 0.76. − IR ($CHCl_3$): $\tilde{\nu}$ = 2947 cm^{-1} (m), 1442 (w), 1353 (m), 1121 (s), 1077 (m), 1035 (m), 976 (m), 904 (w), 869 (w). − ^{1}H NMR (400 MHz): δ = 1.51−1.86 (m, 6 H, 3 CH_2), 2.52−2.65 (m, 1 H, 2′-H), 3.34−3.45 (m, 2 H, CH_2I), 3.52−3.58 (m, 1 H, 6-H), 3.59−3.68 (m, 1 H, 1′-H), 3.81−3.91 (m, 1 H, 6-H), 4.01−4.09 (m, 1′-H), 4.66 (m, 1 H, 2-H). − ^{13}C NMR (100 MHz): δ = 124.59 (q, $J_{(C,F)}$ = 281.7, CF_3), 99.00 (d), 98.84 (d), 63.91 (t), 63.46 (t), 62.07 (t), 61.68 (t), 46.19 (qd, $J_{(C,F)}$ = 25.9), 45.97 (qd, $J_{(C,F)}$ = 25.7), 30.31 (t), 30.23 (t), 25.37 (t), 19.03 (t), 18.78 (t), −4.06 (t), −4.25 (t). − ^{19}F NMR: δ = −68.35 (d, $J_{(H,F)}$ = 8.6, CF_3), −68.38 (d, $J_{(H,F)}$ = 9.6, CF_3). − EI MS; *m*/*z* (%): 337 (16) [(M − 1)$^+$], 280 (3), 254 (6), 237 (42), 211 (12), 193 (1), 173 (3), 155 (36), 141 (9), 127 (13), 109 (23), 95 (2), 85 (100), 56 (3). − $C_9H_{14}F_3IO_2$ (338.11): calcd. C 31.97, H 4.17; found C 32.08, H 4.24.

(2′*S*,2″*RS*)-3-(Tetrahydropyran-2-yloxy)-2-(trifluoromethyl)propyl Toluene-4-sulfonate (19): *p*-Toluenesulfonyl chloride (TosCl, 0.382 g, 2.00 mmol) and 4-pyrrolidinopyridine (ca. 5 mg) were added to a cold solution (0°C) of alcohol **17** (0.501 g, 2.19 mmol)[46] in CH_2Cl_2 (1.0 mL). Pyridine (0.36 mL, 4.42 mmol) was added at 0°C within 30 min and the mixture was stirred overnight at r.t., then poured onto ice/water (10 mL) and extracted with Et_2O (3 × 15 mL). Drying ($MgSO_4$), concentration by RV and under HV and purification by FC (pentane/Et_2O, 4:1) afforded **19** (0.341 g, 41%). − R_f (pentane/Et_2O, 2:1) = 0.42. − IR ($CHCl_3$): $\tilde{\nu}$ = 2947 cm^{-1} (m), 1598 (w), 1442 (2), 1370 (m), 1256 (w), 1144 (m), 1097 (w),

1078 (w), 1035 (m), 990 (m), 903 (w), 869 (w). − ^{1}H NMR (400 MHz): δ = 1.47−1.74 [m, 6 H, 3 CH_2 (THP)], 2.45 (s, 3 H, Ph−CH_3), 2.70−2.76 (m, 2′-H), 3.47−3.57 (m, 2 H, 3′-H, 6″-H), 3.71−3.76 (m, 1 H, 6″-H), 3.91 (dd, J = 10.5 and 6.0, 0.5 H, 3′-H_A), 3.96 (dd, J = 10.4 and 4.5, 0.5 H, 3′-H_B), 4.25−4.33 (m, 2 H, 2 1′-H), 4.52−4.54 (m, 1 H, 2″-H), 7.36 (d, J = 8.4, 2 H, arom. H), 7.80 (d, J = 8.4, 2 H, arom. H). − ^{13}C NMR (100 MHz): δ = 145.21 (s), 145.18 (s), 132.45 (s), 129.96 (d), 129.94 (d), 128.04 (d), 124.75 (q, $J_{(C,F)}$ = 276.5, CF_3), 99.32 (d), 98.51 (d), 63.99 (t), 63.97 (t), 62.18 (t), 61.69 (t), 61.09 (t), 60.57 (t), 44.38−43.60 (2 dq), 30.21 (t), 30.10 (t), 25.28 (t), 25.26 (t), 21.67 (q), 19.12 (t). − ^{19}F NMR: δ = −67.62 (2 d,[47] CF_3). − EI MS; *m/z* (%): 383 (1) [(M + 1)$^+$], 364 (1), 324 (< 1), 298 (3), 281 (14), 259 (< 1), 234 (< 1), 211 (3), 173 (37), 155 (100), 139 (3), 101 (9), 91 (33), 85 (58), 65 (3), 56 (1). − $C_{16}H_{21}F_3O_5S$ (382.4): calcd. C 50.26, H 5.54; found C 50.02, H 5.64.

General Procedure for the Addition of the Lithium Derivative 20 to Carbonyl Compounds (GP1 and GP2). − GP1: A cold solution (−105°C) of the iodide (ca. 0.9 mmol) in Et_2O (5 mL) was slowly treated with 2.0 equiv. of *t*BuLi and stirred for 5 min. A solution of the carbonyl compound (1.0 equiv.) in Et_2O (5 mL) was slowly added and the resulting mixture was stirred for 1.5 h at −105°C, then for 0.5−1 h at −100°C and then quenched with saturated aqueous NH_4Cl (5 mL). The mixture was allowed to warm to r.t. and extracted with Et_2O (3 × 20 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Subsequent purification by FC (pentane/Et_2O, 2:1) resulted in the pure product. − **GP2:** The procedure was similar to GP1 with the only difference that the mixture resulting after the addition of the carbonyl compound was allowed to warm to −78°C overnight.

***rac*-1-Phenyl-4-(tetrahydropyran-2-yloxy)-3-(trifluoromethyl)-butan-1-ol (21):** According to GP1, iodide *rac*-**18** (0.305 g, 0.902 mmol) was treated with *t*BuLi (1.2 mL, 1.80 mmol) and benzaldehyde (0.090 mL, 0.891 mmol) yielding alcohol **21** (0.210 g, 73%). − R_f (pentane/Et_2O, 2:1) = 0.24. − For IR, ^{1}H and ^{19}F NMR, EI MS, and elemental analysis see Supporting Information.

***rac*-1,1-Diphenyl-4-(tetrahydropyran-2-yloxy)-3-(trifluoromethyl)propan-1-ol (22):** According to GP2, iodide *rac*-**18** (0.305 g, 0.901 mmol) was treated with *t*BuLi (1.5 mL, 1.95 mmol) and benzophenone (179 mg, 0.98 mmol). Purification by FC (pentane/Et_2O, 3:1) yielded alcohol **22** (0.247 g, 69%). − R_f (pentane/Et_2O, 2:1) = 0.50. − For IR, ^{1}H, ^{13}C, and ^{19}F NMR, EI MS and elemental analysis see Supporting Information.

***rac*-2-Phenyl-5-(tetrahydropyran-2-yloxy)-4-(trifluoromethyl)-pentan-2-ol (23):** According to GP1, iodide *rac*-**18** (0.295 g, 0.872 mmol) was treated with *t*BuLi (1.2 mL, 1.8 mmol) and acetophenone (0.103 mL, 0.881 mmol). Purification by FC (pentane/Et_2O, 3:1) yielded alcohol **23** (0.137 g, 47%). − R_f (pentane/Et_2O, 2:1) = 0.15. − For IR, ^{1}H and ^{19}F NMR, EI MS, and elemental analysis see Supporting Information.

***rac*-1-[3-(Tetrahydropyran-2-yloxy)-2-(trifluoromethyl)propyl]-cyclohexanol (24):** According to GP1, iodide *rac*-**18** (0.267 g, 0.790 mmol) was treated with *t*BuLi (1.1 mL, 1.6 mmol) and cyclohexanone (0.082 mL, 0.792 mmol). Purification by FC (pentane/Et_2O, 3:1) yielded alcohol **24** (0.140 g, 57%). − R_f (pentane/Et_2O, 2:1) = 0.23. − For IR, ^{1}H, ^{13}C, and ^{19}F NMR, EI MS and elemental analysis see Supporting Information.

***rac*-2-Methyl-5-(tetrahydropyran-2-yloxy)-4-(trifluoromethyl)-pentan-2-ol (25):** According to GP2, iodide *rac*-**18** (0.309 g, 0.912 mmol) was treated with *t*BuLi (1.50 mL, 1.92 mmol) and acetone (0.080 mL, 1.090 mmol), which was added without being diluted. Purification by FC (pentane/Et_2O, 1:1) yielded alcohol **25** (0.127 g, 51%). − R_f (pentane/Et_2O, 3:1) = 0.23. − For IR, ^{1}H, ^{13}C, and ^{19}F NMR, EI MS and elemental analysis see Supporting Information.

(2*R*,2′*RS*,4*RS*)-9-Benzyloxy-1-(tetrahydropyran-2-yloxy)-2-(trifluoromethyl)nonan-4-ol (26): According to GP1, iodide **18** (1.076 g, 3,18 mmol) was treated with *t*BuLi (5.1 mL, 6.68 mmol) and 6-benzyloxyhexanal (0.662 g, 3.21 mmol) to afford alcohol **26** (0.556 g, 42%). − R_f (pentane/Et_2O, 2:1) = 0.11. − For IR, ^{1}H and ^{19}F NMR, EI MS, and elemental analysis see Supporting Information.

(2*R*,2′*RS*,4*RS*)-7-Benzyloxy-1-(tetrahydropyran-2-yloxy)-2-(trifluoromethyl)heptan-4-ol (27): According to GP2, iodide **18** (0.302 g, 0.893 mmol) was treated with *t*BuLi (1.3 mL, 1.92 mmol) and 4-benzyloxybutanal (0.191 g, 1.01 mmol) yielding alcohol **27** (0.205 g, 59%). − R_f (Et_2O/pentane, 2:1) = 0.34. − For IR, ^{1}H and ^{19}F NMR, EI MS, and elemental analysis see Supporting Information.

(2′*RS*,4*RS*,6*R*)-2-Methyl-7-(tetrahydropyran-2-yloxy)-6-(trifluoromethyl)hept-2-en-4-ol (28): According to GP1, iodide **18** (0.340 g, 1.01 mmol) was treated with *t*BuLi (1.4 mL, 2.15 mmol) and 3-methyl-2-butenal (0.117 g, 1.39 mmol). Purification by FC (pentane/Et_2O, 2:1) yielded alcohol **28** (0.149 g, 50%). − R_f (pentane/Et_2O, 2:1) = 0.18. − For IR, ^{1}H and ^{19}F NMR, EI MS, and elemental analysis see Supporting Information.

(2′*RS*,3*R*)-4,4,4-Trifluoro-3-(tetrahydropyran-2-yloxymethyl)-3-butyraldehyde (29): A cold solution (−105°C) of iodide **18** (11.90 g, 35.2 mmol) in Et_2O (200 mL) was treated with *t*BuLi (59.1 mL, 73.9 mmol) within 30 min and stirred for 10 min. DMF (5.4 mL, 70 mmol) was added such that the temperature remained below −105°C. After stirring overnight while allowing to warm to −78°C, then to −20°C (within 2 h), saturated aqueous NH_4Cl (100 mL) was added. The phases were separated and the aqueous layer was additionally extracted with Et_2O (3 × 80 mL). The combined organic. layers were dried ($MgSO_4$) and the solvent was removed (RV). Purification by FC (pentane/Et_2O, 2:1) resulted in **29** (6.56 g, 78%) as a colorless oily mixture of the two enantiomerically pure diastereoisomers. − R_f (pentane/Et_2O, 2:1) = 0.27. − IR ($CHCl_3$): $\tilde{\nu}$ = 2946 cm^{-1} (m), 2857 (w), 2735 (w), 1729 (s), 1454 (w), 1442 (w), 1386 (m), 1257 (s), 1130 (s), 1076 (m), 1062 (m), 1035 (s), 972 (m), 908 (m), 870 (w). − ^{1}H NMR (400 MHz): δ = 1.49−1.81 [m, 6 H, 3 CH_2 (THP-PG)], 2.67−2.85 (m, 2 H, 2-H), 3.06−3.21 (m, 1 H, 3-H), 3.47 (dd, J = 10.2, 7.0, 0.5 H, 4-H_A), 3.49−3.55 (m, 1 H, 6′-H), 3.63 (dd, J = 10.1, 4.8, 0.5 H, 4-H_B), 3.73−3.80 (m, 1 H, 6′-H), 3.83 (dd, J = 10.1, 7.0, 0.5 H, 4-H_B), 4.01 (dd, J = 10.2, 4.8, 0.5 H, 4-H_A), 4.58 (m, 1 H, 2′-H), 9.76 (s, 1 H, CHO)$_)$. − ^{13}C NMR (100 MHz): δ = 198.11 (d), 126.62 (q, $J_{(C,F)}$ = 278.7, CF_3), 99.35 (d), 98.54 (d), 64.05 (t), 63.48 (t), 62.34 (t), 61.87 (t), 39.89 (t), 38.67 (qd, J = 27.7), 38.41 (dq, J = 26.79), 30.23 (t), 30.19 (t), 25.28 (t), 19.22 (t), 18.88 (t). − ^{19}F NMR: δ = −69.71 (d, $J_{(H,F)}$ = 7.5, CF_3), −69.73 (d, $J_{(H,F)}$ = 7.5, CF_3). − EI MS; *m/z* (%): 240 (< 1) [M$^+$], 239 (< 1), 222 (1), 210 (< 1), 196 (9), 182 (< 1), 165 (2), 155 (4), 139 (100), 101 (3), 91 (6), 85 (11). − $C_{10}H_{15}F_3O_3$ (240.22): calcd. C 50.00, H 6.29; found C 50.02, H 6.14.

Methyl (1*RS*,2′*R*,2″*RS*)-*O*-[1-(3-Benzyloxypropyl)-4,4,4-trifluoro-3-(tetrahydropyran-2-yloxymethyl)butyloxy]carbodithioate (30): A solution of alcohol **27** (0.120 g, 0.307 mmol) in THF (5 mL) was treated with NaH (25 mg, 0.575 mmol, suspension) and stirred at r.t. CS_2 (0.20 mL, 3.31 mmol) was added after 30 min, then 14 h later MeI (0.20 mL, 3.18 mmol) and 11 h later saturated aqueous $NaHCO_3$ (5.0 mL). The aqueous layer was extracted (Et_2O, 3 × 20 mL), the combined organic layers were dried ($MgSO_4$) and the solvent was removed (RV and HV). Subsequent purification by FC (pentane/Et_2O, 4:1) yielded the pure product **30** (0.127 g, 86%). − R_f (pentane/Et_2O, 2:1) = 0.74. − IR ($CHCl_3$): $\tilde{\nu}$ = 2946 cm^{-1} (m),

2863 (w), 1454 (w), 1356 (w), 1169 (m), 1127 (m), 1054 (s), 975 (w), 907 (w), 869 (w). – ^{1}H NMR (400 MHz): δ = 1.43–2.17 (m, 12 H, 6 CH_2), 2.35–2.54 (m, 1 H, H–C–CF_3), 2.55 (s, 3 H, SCH_3), 3.43–3.55 (m, 4 H, CH_2–OBn, CH_2–O–), 3.75–3.84 (m, 1 H, *H*–CH–O–), 3.86–3.99 (m, 1 H, H–C*H*–O–), 4.49 (s, 2 H, benz. H), 4.57–4.62 (m, 1 H, –O–CH–O–), 5.89–5.99 {m, 1 H, H–C–O[C(S)SMe]}, 7.27–7.36 (m, 5 H, arom. H). – ^{19}F NMR: δ = –69.36 (d, $J_{(H,F)A}$ = 8.6, CF_3), –69.43 (d, $J_{(H,F)B}$ = 8.6, CF_3), –69.60 (d, $J_{(H,F)C}$ = 8.5, CF_3), –69.64 (d, $J_{(H,F)D}$ = 8.6, CF_3). – EI MS; *m*/*z* (%): 480 (< 1) [M^+], 465 (< 1), 433 (< 1), 395 (< 1), 363 (< 1), 349 (< 1), 305 (< 1), 289 (6), 271 (< 1), 229 (< 1), 197 (5), 181 (14), 163 (1), 152 (1), 139 (9), 120 (1), 107 (8), 91 (100), 85 (82). – $C_{22}H_{31}F_3O_4S_2$ (480.61): calcd. C 54.98, H 6.50; found C 54.81, H 6.44.

(2*RS*,2′*R*)-2-[7-Benzyloxy-2-(trifluoromethyl)heptyloxy]-tetrahydropyran (31): To a hot solution (80°C) of tributyltin hydride (0.070 mL, 0.264 mmol) and AIBN (5 mg, 0.030 mmol) in toluene (1.8 mL), a solution of dithiocarbonate **30** (0.107 g, 0.223 mmol) in toluene (1.3 mL) was added within 1 h and the resulting mixture was stirred at 80°C overnight. The solvent was evaporated (RV and under HV) and the residue was purified by FC (pentane → pentane/Et_2O, 4:1), yielding a mixture of the starting material **30** (9.2 mg, 9%, by ^{1}H NMR) which could not be separated by FC and the product **31** (58.3 mg, 70%, by ^{1}H NMR). – R_f (pentane/Et_2O, 2:1) = 0.53. – IR ($CHCl_3$): $\tilde{\nu}$ = 2944 cm^{-1} (s), 2868 (m), 1496 (w), 1454 (m), 1356 (m), 1167 (s), 1129 (s), 1077 (m), 1031 (s), 907 (w), 869 (w). – ^{1}H NMR (400 MHz): δ = 1.35–1.89 (m, 14 H, 7 CH_2), 2.25–2.36 (m, 1 H, 2′-H), 3.40–3.54 (m, 2 H, 1′-H, 6-H), 3.46 (t, *J* = 6.5, 2 H, 7′-H), 3.78–3.84 (m, 1.5 H, 1′-H_A, 6-H), 3.92 (dd, *J* = 10.4 and 5.3, 0.5 H, 1′-H_B), 4.49 (s, 2 H, benz. H), 4.57–4.61 (m, 1 H, 2-H), 7.25–7.36 (m, 5 H, arom. H). – ^{13}C NMR (100 MHz): δ = 138.64 (s), 128.37 (d), 127.63 (d), 127.63 (q, $J_{(C,F)}$ = 280.7, CF_3), 127.53 (d), 98.88 (d), 98.87 (d), 72.93 (t), 70.24 (t), 64.46 (t), 64.40 (t), 43.58 (qd, $J_{(C,F)}$ = 24.8), 43.51 (qd, $J_{(C,F)}$ = 25.0), 30.43 (t), 29.53 (t), 26.71 (t), 26.23 (t), 25.57 (t), 25.41 (t), 19.14 (t). – ^{19}F NMR: δ = –69.02 (d, $J_{(H,F)A}$ = 10.7, CF_3), –69.12 (d, $J_{(H,F)B}$ = 10.7, CF_3). – EI MS; *m*/*z* (%): 373 (1) [$(M - 1)^+$], 318 (< 1), 289 (21), 271 (< 1), 181 (1), 163 (< 1), 147 (2), 123 (1), 107 (35), 91 (100), 85 (81), 65 (5), 55 (7), 41 (11).

(2′*RS*,3*R*)-4-(Tetrahydropyran-2-yloxy)-3-(trifluoromethyl)butan-1-ol (32): To a suspension of $NaBH_4$ (1.20 g, 31.7 mmol) in Et_2O (7.8 mL), a solution of aldehyde **29** (6.28 g, 26.1 mmol) in Et_2O (5.2 mL) and MeOH (1.0 mL) was added at 0°C. The mixture was stirred for 20 min, then quenched with saturated aqueous $NaHCO_3$ (35 mL) and stirred for another 1.5 h. $NaHCO_3$ (100 mL) was added and stirring was continued for 1 h. The aqueous layer was extracted with Et_2O (3 × 70 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed by RV and the crude product was purified by FC (Et_2O/pentane/Et_3N, 75:24:1) yielding the pure and colorless alcohol **32** (5.07 g, 80%). – R_f (Et_2O/pentane/Et_3N, 75:24:1) = 0.25. – IR ($CHCl_3$): $\tilde{\nu}$ = 3456 cm^{-1} (m, br.), 2948 (m) 1454 (w), 1442 (w), 1386 (m), 1354 (m), 1335 (m), 1257 (s), 1171 (s), 1128 (s), 1076 (m), 1058 (m), 1032 (s), 908 (w), 870 (w). – ^{1}H NMR (400 MHz): δ = 1.51–1.86 (m, 7 H, 3 CH_2, H–C–H), 1.96–2.06 (m, 1 H, H–C–*H*), 2.16–2.23 (m, 1 H, OH), 2.52–2.68 (m, 1 H, 3-H), 3.49–3.57 (m, 1.5 H, 4-H_A and 6′-H), 3.65 (dd, *J* = 10.2 and 4.2, 0.5 H, 4-H_B), 3.71–3.89 (m, 3.5 H, 2 1-H, 4-H_B and 6′-H), 4.03 (dd, *J* = 10.4 and 4.1, 0.5 H, 4-H_A), 4.62 (m, 1 H, 2′-H). – ^{13}C NMR (100 MHz): δ = 127.3 (q, $J_{(C,F)}$ = 279.9, CF_3), 99.62 (d), 99.16 (d), 65.20 (t), 64.76 (t), 62.62 (t), 62.36 (t), 60.04 (t), 59.97 (t), 41.25 (qd, *J* = 25.4), 41.11 (qd, *J* = 25.5), 30.47 (t), 30.38 (t), 29.43 (t), 29.41 (t), 25.26 (t), 19.45 (t), 19.27 (t). – ^{19}F NMR: δ = –69.62 (d, $J_{(H,F)}$ = 10.7, $CF_{3(Diast.\ 1)}$), –69.56 (d, $J_{(H,F)}$ = 10.7, $CF_{3(Diast.\ 2)}$). – EI MS; *m*/*z* (%): 241 (1) [$(M - 1)^+$], 184 (4), 169 (4), 156 (2), 141 (100), 123 (12), 121 (19), 101 (16), 91 (10), 85 (24). – $C_{10}H_{17}F_3O_3$ (242.24): calcd. C 49.58, H 7.07; found C 49.53, H 7.07.

(2″*RS*,3′*R*)-4-(Tetrahydropyran-2-yloxy)-3-(trifluoromethyl)butyl *p*-Toluenesulfonate (33): Alcohol **32** (4.89 g, 20.2 mmol) was dissolved in pyridine (85 mL) and cooled to 0°C and the resulting solution was treated with TosCl (20.0 g, 105.0 mmol). The mixture was stirred at –10°C until it became homogeneous and then stored at –20°C. After 48 h, it was poured onto ice/water (300 mL) and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and then dried ($MgSO_4$). The solvent was removed and the residue was purified by FC (pentane/Et_2O, 2:1) to afford tosylate **33** (6.00 g, 75%).[49] – R_f (pentane/Et_2O, 2:1) = 0.28. – IR ($CHCl_3$): $\tilde{\nu}$ = 2947 (m), 1599 (w), 1442 (w), 1364 (m), 1129 (m), 1098 (w), 1077 (w), 1034 (m), 973 (m), 900 (w). – ^{1}H NMR (400 MHz): δ = 1.49–1.78 [m, 6 H, 3 CH_2 (THP)], 1.95–2.08 (m, 2 H, 2′-H), 2.45 (s, 3 H, Ph–CH_3), 2.43–2.51 (m, 1 H, 3′-H), 3.44 (dd, *J* = 10.5 and 5.6, 0.5 H, 4′-H_A), 3.46–3.53 (m, 1.5 H, 4′-H_B and 6″-H), 3.72–3.77 (m, 1 H, 6″-H), 3.81 (dd, *J* = 10.4 and 6.1, 0.5 H, 4′-H_B), 3.88 (dd, *J* = 10.5 and 4.5, 0.5 H, 4′-H_A), 4.18 (t, *J* = 6.4, 2 H, 1′-H), 4.52–4.54 (m, 1 H, 2″-H), 7.35 (d, *J* = 8.5, 2 H, arom. H), 7.79 (d, *J* = 8.5, 2 H, arom. H). – ^{13}C NMR (100 MHz): δ = 144.99 (s), 144.97 (s), 132.94 (s), 129.92 (d), 127.92 (d), (q, $J_{(C,F)}$ = 280.16, CF_3), 99.24 (d), 98.61 (d), 67.50 (t), 67.44 (t), 63.93 (t), 63.57 (t), 62.32 (t), 61.86 (t), 40.17 (qd, *J* = 25.8), 40.05 (qd, *J* = 25.9), 30.34 (t), 30.26 (t), 25.54 (t), 25.31 (t), 21.65 (q), 19.27 (t), 18.96 (t). – ^{19}F NMR: δ = –69.24 (d, $J_{(H,F)}$ = 10.7, CF_3), –69.29 (d, $J_{(H,F)}$ = 10.7, CF_3). – EI MS; *m*/*z* (%): 396 (< 1 [M^+]), 395 (< 1), 378 (< 1), 341 (< 1), 313 (1), 295 (1), 284 (4), 282 (3), 262 (2), 246 (7), 216 (2), 174 (12), 173 (100), 172 (67), 169 (34), 155 (63), 139 (44), 107 (3), 91 (18). – $C_{17}H_{23}F_3O_5S$ (396.43): calcd. C 51.51, H 5.85; found C 51.39, H 5.69.

(2*RS*,2′*R*)-2-[6-Methyl-2-(trifluoromethyl)hept-5-enyloxy]-tetrahydropyran (34): 1-Bromo-2-methyl-1-propene (0.73 mL, 7.24 mmol) was dissolved in THF (7.5 mL) and cooled to –78°C. *t*BuLi (9.1 mL, 14.11 mmol)[24] was added within 30 min and the resulting mixture was stirred for 3 h at that temperature. It was allowed to warm to –50°C within a few minutes, then recooled to –78°C and treated with CuCN (0.324 g, 3.62 mmol) under a positive pressure of argon. The inhomogeneous mixture was allowed to warm to –20°C and the resulting 2-phase mixture of two liquids was cooled again to –78°C. Addition of the tosylate **31** (1.454 g, 3.62 mmol) resulted in a clear solution, which was allowed to warm to r.t. within 1 h and stirred overnight. The resulting dark brown solution was treated with saturated aqueous $NaHCO_3$ (40 mL) and extracted with Et_2O (4 × 50 mL). Drying of the combined organic layers ($MgSO_4$), evaporation of the solvent and purification by FC [pentane/Et_2O, 19:1; R_f (pentane/Et_2O, 2:1) = 0.65] yielded a mixture (0.887 g, 87%) of **34** and the saturated derivative **35** (81:19) which could not be separated by FC and which was used without any further purification in the subsequent reactions.

(*R*)-6-Methyl-2-(trifluoromethyl)hept-5-en-1-ol (36): A solution of crude **34** (1.669 g, 5.95 mmol[50]) was dissolved in MeOH (40 mL). DOWEX 50 W (ca. 100 mg) was added and the resulting mixture was stirred overnight at r.t. After filtration, the solvent was removed and filtration [SiO_2; pentane/Et_2O, 9:1; R_f (pentane/Et_2O, 2:1) = 0.39] and cautious drying yielded a mixture (0.935 g) of ether containing **36** and its corresponding byproduct, which was directly used in the subsequent step.

(*S*)-7,7,7-Trifluoro-6-iodomethyl-2-methylhept-2-ene (37): By analogy to the procedure of Lange and Gottardo,[37] triphenylphos-

phane (1.279 g, 4.87 mmol) was dissolved in CH_2Cl_2 (12.7 mL) and treated with imidazole (668 mg, 9.99 mmol), iodine (1.159 g, 4.57 mmol) and a solution of alcohol **36** (0.901 g, ca. 3.75 mmol[51]) in CH_2Cl_2 (3.5 mL) and stirred for 7 h at r.t. The solvent was removed (RV) and the crude mixture was filtered through silica gel [pentane; R_f (pentane) = 0.50] and cautiously dried (product is rather volatile!) resulting in crude **37** (1.439 g) which was directly used in the subsequent step.

(*R*)-7-Methyl-3-(trifluoromethyl)oct-6-enal (39): The solution of the crude iodide **37** (1.415 g, ca. 3.73 mmol of iodide[51]) in Et_2O (20 mL) was lithiated with *t*BuLi (5.2 mL, 7.84 mmol) at −105°C, stirred for 7 min and subsequently treated with DMF (0.6 mL, 7.5 mmol). The resulting mixture was stirred overnight while allowing to warm to −78°C, then to −20°C within 1 h, quenched with saturated aqueous NH_4Cl (20 mL) and then allowed to warm to r.t. Separation of the phases, extraction of the aqueous layer with Et_2O (4 × 30 mL) and purification by FC [pentane/Et_2O, 2:1; R_f (pentane/Et_2O, 2:1) = 0.54] resulted in an ethereal, smelling solution, somewhat like *melissa officinalis*, of crude **39** (1.387 g), which was directly used in the subsequent reduction step.

(*R*)-7-Methyl-3-(trifluoromethyl)oct-6-en-1-ol [(*R*)-Trifluorocitronellol, (*R*)-(+)-2b]. − (A) Reduction of 39: A solution of crude aldehyde **39** (1.303 g, ca. 3.53 mmol[51]) in Et_2O (10 mL) was added to a cold suspension (0°C) of $NaBH_4$ (67 mg, 1.77 mmol) in Et_2O (10 mL) and MeOH (1.0 mL). The resulting mixture was stirred for 30 min at r.t. and then treated with saturated aqueous $NaHCO_3$ (20 mL). The phases were separated and the aqueous layer was additionally extracted with Et_2O (5 × 30 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed (RV). Purification by FC (pentane/Et_2O, 4:1) resulted in the crude product **2b** (0.875 g). For purification purposes, the crude alcohol **2b** was esterified (→ **40**). − **(B) Esterification of Crude 2b To Give (*R*)-6-Methyl-3-(trifluoromethyl)oct-6-enyl Octanoate (40) and Separation of the Impurity Derived from 35:** A solution of crude **2b** (0.875 g, ca. 3.5 mmol) in CH_2Cl_2 (10 mL) was cooled to 0°C and treated with octanoyl chloride (0.80 mL, 4.67 mmol). Pyridine (0.5 mL, 6.24 mmol) was added within 20 min and the resulting mixture was stirred for 15 min at 0°C, then 12 h at r.t. The solution was diluted with Et_2O to 60 mL and washed with saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous NaCl (30 mL). Drying of the organic layer ($MgSO_4$), removing of the solvent and filtering through silica gel (pentane/Et_2O, 4:1) resulted in a mixture of **2b** and the corresponding aliphatic derivative (from **35**). The separation of these two was achieved with mercury acetate.[32] The mixture (0.955 g, ca. 2.8 mmol) was dissolved in MeOH (46 mL), H_2O (2.0 mL)/HOAc (0.2 mL) and treated with $Hg(OAc)_2$ (1.78 g, 5.39 mmol). The resulting mixture was vigorously stirred until homogeneity was achieved and stored at r.t. in the dark (48 h) until the olefinic compound was no longer detected by ^1H NMR. The solution was extracted with isooctane (15 × 20 mL) and the methanolic phase was treated with 30% aqueous HCl (6.25 mL) and stirred for 10 min. The acidic mixture was diluted with H_2O to a total volume of 100 mL and extracted with hexane (4 × 50 mL). The hexane phase was dried ($MgSO_4$) and the solvent was removed (RV). The residue was purified twice by FC (pentane/Et_2O, 9:1). Removal of the solvent by RV and under HV yielded pure ester **40** (0.286 g, 14% from **33**[50]) as a colorless oil. − R_f (pentane/Et_2O, 2:1) = 0.64. − $[\alpha]_D^{r.t.}$ = −1.13 (*c* = 0.975, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 2930 cm^{-1} (s), 2857 (m), 1730 (s), 1459 (m), 1379 (w), 1259 (m), 1160 (s), 1124 (m), 1034 (w). − ^1H NMR (400 MHz): δ = 0.86 (t, *J* = 6.9, 3 H, 8-H), 1.23−1.32 (m, 8 H, 2 4-H, 2 5-H, 2 6-H, 2 7-H), 1.41−1.50 (m, 1 H, 4′-H), 1.54−1.80 (m, 4 H, 2′-H, 2 3-H, 4′-H), 1.61 (s, 3 H, Me), 1.70 (s, 3 H, Me), 1.91−1.99 (m, 1 H, 2′-H), 2.01−2.12 (m, 2 H, 5′-H), 2.13−2.25 (m, 1 H, 3′-H), 2.29 (t, *J* = 7.41, 2 H, 2-H), 4.15 (t, *J* = 6.8, 2 H, 1′-H), 5.03−5.08 (m, 1 H, 6′-H). − ^{13}C NMR (100 MHz): δ = 173.67 (s), 133.03 (s), 128.36 (q, $J_{(C,F)}$ = 280.0, CF_3), 122.92 (d), 61.49 (t), 39.19 (qd, *J* = 25.4), 34.28 (t), 31.66 (t), 29.12 (t), 28.93 (t), 28.00 (t), 27.19 (t), 25.69 (q), 25.14 (t), 24.96 (t), 22.60 (t), 17.71 (q), 14.05 (q). − ^{19}F NMR: δ = −70.20 (d, $J_{(H,F)}$ = 8.54, CF_3). − EI MS; *m/z* (%): 337 (1) [(M + 1)$^+$], 265 (< 1), 209 (< 1), 192 (46), 177 (100), 163 (27), 145 (18), 135 (20), 95 (5), 81 (3), 57 (3). − $C_{18}H_{31}F_3O_2$ (336.44): calcd. C 64.26, H 9.29; found C 64.44, H 9.45. − **(C) Saponification of Benzoate 40:** A solution of ester **40** (0.247 g, 0.734 mmol) in THF (8.0 mL) was treated with 4.4 mL (4.4 mmol) of 1 N aqueous LiOH and stirred overnight at r.t. Saturated aqueous $NaHCO_3$ (5.0 mL) was added and the mixture was extracted with Et_2O (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed. Purification (2 ×) by FC (pentane/Et_2O, 3:1) followed by drying under HV yielded the pure product **2b** (0.122 g, 80%) as a colorless oil with a characteristic odor. − R_f (pentane/Et_2O, 2:1) = 0.22. − $[\alpha]_D^{r.t.}$ = +0.83 (*c* = 1.03, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}$ = 3626 cm^{-1} (m), 3442 (w, br.), 2934 (m), 1671 (w), 1452 (m), 1384 (m), 1338 (w), 1263 (m), 1151 (s), 1116 (s), 1048 (m), 838 (w). − ^1H NMR (400 MHz): δ = 1.36 (s, br., 1 H, OH), 1.40−1.49 (m, 1 H, 4-H), 1.61 (s, 3 H, Me), 1.64−1.77 (m, 2 H, 2-H and 4-H), 1.70 (s, 3 H, Me), 1.84−1.93 (m, 1 H, 2-H), 2.02−2.18 (m, 2 H, 5-H), 2.19−2.31 (m, 1 H, 3-H), 3.71−3.75 (m, 2 H, 1-H), 5.05−5.10 (m, 1 H, 6-H). − ^{13}C NMR (100 MHz): δ = 132.94 (s), 128.65 (q, $J_{(C,F)}$ = 280.0, CF_3), 123.15 (d), 60.13 (t), 38.77 (qd, *J* = 25.5), 31.07 (t), 28.20 (t), 25.69 (q), 25.26 (t), 17.71 (q). − ^{19}F NMR: δ = −70.06 (d, $J_{(H,F)}$ = 8.5, CF_3). − EI MS; *m/z* (%): 210 (22) [M$^+$], 192 (41), 177 (100), 163 (27), 157 (1), 149 (21), 135 (40), 129 (4), 123 (6), 109 (6), 95 (15), 82 (21), 69 (78), 56 (16), 41 (23). − $C_{10}H_{17}F_3O$ (210.24): calcd. C 57.13, H 8.15; found C 57.30, H 8.45.

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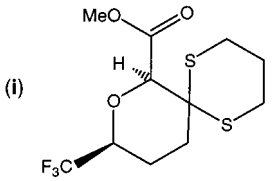
[11] The hydroxy ester **8** was prepared in view of the possibility of forming the macrodiolide **10a** in a stepwise manner.
[12] The desilylations (**6** → **8** or **7** → **9**) had to be carried out with $C_5H_5N{\cdot}HF$; with Bu_4NF the hydroxy ester **8** underwent cyclization to a mixture of THP derivatives of which the *cis* isomer (**i**) was fully characterized: Methyl (7*S*,9*S*)-9-Trifluoromethyl-8-oxa-1,5-dithiaspiro[5.5]undec-7-ylcarboxylate: M.p. 66.0−66.5°C. − $C_{12}H_{17}F_3O_2S_2$ (330.4): calcd. C 43.63, H 5.19, found C 43.90, H 5.48.

(i)



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[16] When this reaction was carried out in MeOH/$CHCl_3$ (4:3), mono- (7%) and diketals (82%) of **1d** were formed. The latter, (3*E*,11*E*,8*S*,16*S*)-5,5,13,13-tetramethoxy-8,16-bis(trifluoromethyl)-1,9-dioxocyclohexadeca-3,11-diene-2,10-dione) has a melting point of 175.8−176.2°C and $[\alpha]_D^{r.t.} = -33.4$ (c = 1.05, $CHCl_3$) and was fully characterized.
[17] The highest solubility (1.8 mg/mL, saturated solution at 25°C) was determined in a mixture of $(CF_3)_2CHOH/CH_2Cl_2$ (1.5:1). In boiling acetone the solubility is ca. 1 mg/mL. The poor solubility is responsible for the low yield in the hydrolysis step **10a** → **1d**.
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[23] Compound **17** is a mono-THP derivative of an achiral diol. In its formation, there could have been partial racemization not only by deprotonation next to the CF_3 group, but also by migration of the THP protecting group. In order to determine the enantiopurity of **17**, the free OH group was benzylated, the THP group removed and the resulting (*S*)-2-(trifluoromethyl)-3-benzyloxypropanol analyzed by HPLC on a Chiracel OD® column. The enantiomeric ratio was 99:1, demonstrating that no loss of configurational purity had occurred in the five steps from F_3-*Roche* acid to this propanol derivative.
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[40] Storing the crude product overnight at −20°C did not cause any change in the yield of the product.
[41] Due to the low solubility of **1d**, no satisfactory ^{13}C-NMR spectra could be recorded.
[42] It is interesting that the product was partially reduced under the analytical conditions, which is the reason for the appearance of the masses (M + NH_4 + nH, n = 1−4), see also **10b**.
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[46] An excess of alcohol **17** was used as separation of products from unreacted TosCl is sometimes difficult. Nevertheless, an excess TosCl and pyridine as solvent was later shown to be advantageous.
[47] The signals are only partially resolved.
[48] The signals are not resolved.
[49] The yields ranged from 85 to 75%.
[50] This material was produced from 6.98 mmol of tosylate **33**. The calculation of the overall yield (**33** → **40**) takes into account the losses through analysis.
[51] According to ^{1}H-NMR spectroscopy.

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