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Asymmetric Synthesis of 2-Trifluoromethyl-1,2,3-triols

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The asymmetric synthesis of the 2-trifluoromethylated 1,2,3-triols **5** starting from 2,2-dimethyl-1,3-dioxan-5-one (**1**) is described. The enantiomerically pure α-alkylated dioxanones **3** and **6** were obtained via the SAMP/RAMP hydrazone methodology. Trifluoromethylation of the monoalkylated dioxanones **3** with (trifluoromethyl)trimethylsilane in the presence of TBAF gave the 2-trifluoromethylated acetonide-protected triols **4** in high diastereo-and enantiomeric excesses (*de* ≥ 96 %, *ee* = 92–≥ 98 %) and good overall yields (52–97 %). Finally, deprotection of the triol under acidic conditions afforded the title compound **5** (*de* ≥ 96 %, *ee* = 95, 96 %) as a typical example. In addition, the methodology was extended to the trialkylated dioxanone **6** leading to the trifluoromethylated alcohol **7** with two neighbouring quaternary stereocenters in good yield (77 %) and very good diastereo- and enantiomeric excesses (*de* ≥ 96 %, *ee* = 98 %).

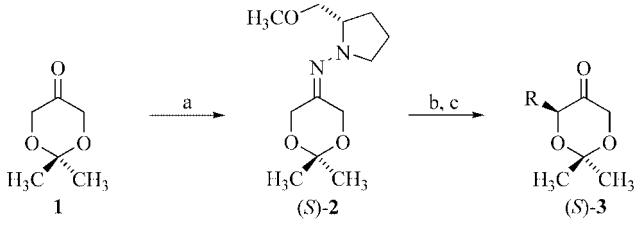
Introduction

Due to the unique properties of fluorinated substances, these compounds are of ever growing interest not only in classical organic chemistry, but also in the material, agrochemical, medicinal and pharmaceutical sciences.[1,2] Characteristic properties of trifluoromethylated substances are an increased lipophilicity, superior metabolic stability and in general significant changes in their physical, chemical and biological properties as compared to the parent methyl compounds.

Often trifluoromethylated biologically active substances are derivatives or analogues of natural compounds. An efficient strategy to synthesize these substances is the introduction of the rather valuable CF_3 group in the final stage of the synthesis. An example for this strategy is the trifluoromethylation of artemisinin, an antimalarial agent.[3] There are several methods (electrophilic, nucleophilic and radical) available for the trifluoromethylation of organic compounds[4] and one of the most common reagents is (trifluoromethyl)trimethylsilane ($TMSCF_3$, Ruppert reagent). First synthesized by Ruppert et al. in 1984,[5] later Prakash et al. investigated its use for nucleophilic trifluoromethylation of carbonyl compounds in detail.[6,7] However, to date, the stereoselective trifluoromethylation with Ruppert reagent is still a synthetic challenge.[2,8,9]

Results and Discussion

As shown in Scheme 1, our synthesis started from the readily available 2,2-dimethyl-1,3-dioxan-5-one (**1**), which can be obtained according to literature procedures on a large scale.[10–11,12] Condensation of **1** with (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) gave the hydrazone (*S*)-**2**, which was alkylated with different electrophiles (RX) in α-position[11,12] according to the SAMP/RAMP hydrazone methodology.[13] Subsequently, the chiral auxiliary was removed without racemization by ozonolysis in dichloro-



Scheme 1. Synthesis of acetonide-protected keto diols (*S*)-**3**. a) SAMP, benzene, reflux, 7 h; b) *t*BuLi, THF, –78 °C, then RX at –100 °C; c) O_3, CH_2Cl_2, –78 °C.

Table 1. Asymmetric synthesis of the protected keto diols (*S*)- and (*R*)-**3**.

3	R	X	Yield[a] [%]	*ee*[b] [%]
(*S*)-**3a**	Me	I	55	94[c]
(*R*)-**3a**[d]	Me	I	57	94[c]
(*S*)-**3b**	Et	I	74	94
(*R*)-**3b**[d]	Et	I	71	94
(*S*)-**3c**	*i*Pr	I	64	93
(*R*)-**3c**[d]	*i*Pr	I	62	94
(*S*)-**3d**	*n*Bu	I	70	92
(*R*)-**3d**[d]	*n*Bu	I	38	93
(*S*)-**3e**	*n*-Hex	Br	68	95
(*R*)-**3e**[d]	*n*-Hex	Br	70	95

[a] Overall yield starting from **1**. [b] Determined by GC_{CSP} (Chirasil-dex). [c] Determined by GC_{CSP} (Lipodex E). [d] RAMP was used as chiral auxiliary.

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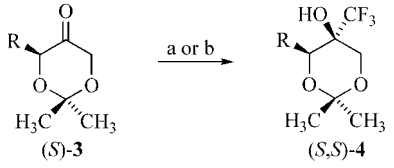
methane. The acetonide-protected keto diols (*S*)- and (*R*)-**3** could be obtained in moderate to good overall yields (38–74%, 3 steps) and very good enantiomeric excesses (*ee* = 92–95%; Table 1), respectively.[11,12]

Although sterically hindered ketones did not react with the Ruppert reagent under nucleophilic 1,2-addition in our hands, we hoped that the enhanced electrophilic character of the dioxanone keto function[14] would allow the envisaged nucleophilic trifluoromethylations and to our delight this indeed turned out to be possible. The diastereoselective trifluoromethylation was carried out by nucleophilic addition of the CF_3 group, easily generated in situ from $TMSCF_3$ and TBAF, to the α-alkylated dioxanones (*S*)-**3a**–**e** affording the dioxanols (*S*,*S*)-**4a**–**e** (Scheme 2, Table 2).



(*S*)-**3** (*S*,*S*)-**4**

Scheme 2. Diastereoselective nucleophilic trifluoromethylation of the protected keto diols (*S*)-**3**. a) 1.5 equiv. $TMSCF_3$, 0.05–0.1 equiv. TBAF, THF, 0 °C; after completion: 1.5 equiv. TBAF, 1 h (method A); b) 1.5 equiv. $TMSCF_3$, 1.5 equiv. TBAF, THF, 0 °C (method B).

Table 2. Nucleophilic trifluoromethylation of the protected keto diols (*S*)- and (*R*)-**3** to afford (*S*,*S*)- and (*R*,*R*)-**4**.

4	R	Method	Yield [%]	*de*[a] [%]	*ee*[b] [%]
(*S*,*S*)-**4a**	Me	B	69	≥ 96	≥ 98
(*R*,*R*)-**4a**	Me	B	59	≥ 96	≥ 98
(*S*,*S*)-**4b**	Et	A	86	≥ 96	93
(*R*,*R*)-**4b**	Et	A	52	≥ 96	93
(*S*,*S*)-**4c**	*i*Pr	B	75	≥ 96	92[c]
(*R*,*R*)-**4c**	*i*Pr	A	73	≥ 96	93[c]
(*S*,*S*)-**4d**	*n*Bu	A	64	≥ 96	94[c]
(*R*,*R*)-**4d**	*n*Bu	A	73	≥ 96	94[c]
(*S*,*S*)-**4e**	*n*-Hex	A	94	≥ 96	95
(*R*,*R*)-**4e**	*n*-Hex	A	97	≥ 96	96

[a] Determined by ^{1}H- and ^{13}C-NMR spectroscopy. [b] Determined by GC_{CSP} (Lipodex E). [c] Determined by GC_{CSP} (Chirasil-dex).

According to literature procedures,[6] $TMSCF_3$ was added at 0 °C to a solution of the dioxanone (*S*)-**3b**, **d** and **e** with a catalytic amount of TBAF (Scheme 2, Table 2, method A). Diastereoselectivity was achieved by using the directing effect of the alkyl group. We expected *Re*-face attack by the nucleophilic CF_3 group leading to the *cis* orientation of the α-alkyl group and the resulting OH group of the acetonide-protected triols **4**. After TMS-deprotection with TBAF, the 5-trifluoromethylated dioxanols (*S*,*S*)-**4b**,**d**,**e** were obtained in good to very good yields (64–94%) and high diastereo and enantiomeric excesses (*de* ≥ 96%, *ee* = 93–95%). The enantiomeric α-trifluoromethylated dioxanols (*R*,*R*)-**4b**–**e** could be obtained in the same way starting from the (*R*)-configured dioxanones (*R*)-**3** in comparable yields and stereoselectivities. For the synthesis of dioxanol **4a** (both enantiomers) and (*S*,*S*)-**4c**, we varied the procedure by adding a stoichiometric amount of TBAF to the solution of dioxanone **3** and $TMSCF_3$. We obtained the deprotected alcohols **4** in good yields (59–75%) and high diastereo and enantiomeric excesses (*de* ≥ 96%, *ee* = 92 to ≥98%). (Scheme 2, Table 2, method B) Stereoselective nucleophilic 1,2-additions to α-alkylated dioxanones are rarely described in literature. Whereas the addition of methyllithium to an α-alkylated dioxanone of type **3** leads to a good diastereomeric excess (*de* = 88%),[15] 1,2-addition of Grignard reagents gave the desired dioxanols in excellent diastereoselectivities (*de* ≥ 99%).[14]

NOE experiments of compound (*S*,*S*)-**4a** confirmed the relative configuration of the two stereocenters (Figure 1). In the chair conformation of the dioxanol ring the hydroxy group is in axial position, whereas the methyl and trifluoromethyl group occupy equatorial positions.

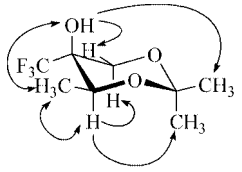
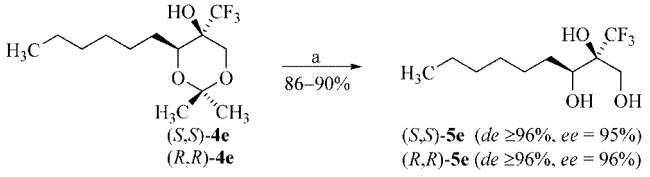


Figure 1. NOE measurements of dioxanol (*S*,*S*)-**4a**.

Finally, we had to demonstrate that the acetonide protecting group of the dioxanols **4** can be easily and efficiently removed to reach the target 2-trifluoromethylated 1,2,3-triols **5**. As a typical example we deprotected both (*S*,*S*)- and (*R*,*R*)-**4e** using freshly activated Dowex 50 in ethanol, respectively. In this manner both enantiomers of 2-(trifluoromethyl)nonane-1,2,3-triol (**5**) were obtained in very good yields (86–90%) and excellent diastereo- and enantiomeric excesses (*de* ≥ 96%; *ee* = 95–96%) (Scheme 3).

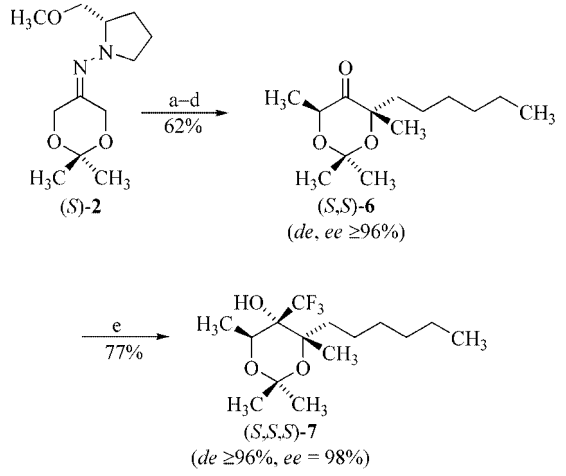


(*S*,*S*)-**4e** (*S*,*S*)-**5e** (*de* ≥96%, *ee* = 95%)
(*R*,*R*)-**4e** (*R*,*R*)-**5e** (*de* ≥96%, *ee* = 96%)

Scheme 3. Cleavage of the acetonide protecting group. a) Dowex 50, ethanol, room temp.

Furthermore, we extended the method to α,α,α′-trialkylated dioxanones as exemplified by (*S*,*S*)-**6**. To synthesize this trialkylated ketone the SAMP-hydrazone (*S*)-**2** was alkylated in α- and α′-position with methyliodide. After a third α-alkylation with *n*-hexyl bromide, the chiral auxiliary was removed by ozonolysis giving the desired trialkylated acetonide-protected keto diol (*S*,*S*)-**6** in 62% yield (4 steps) and excellent diastereo- and enantiomeric excess (*de*, *ee* ≥ 96%) (Scheme 4).[16] The stereoselective trifluoromethylation was carried out again with $TMSCF_3$ in the presence of a catalytic amount of TBAF. Upon the completion of the reaction, 1.5 equiv. TBAF was added and the reaction mixture was stirred for 1 h. The trifluoromethylated dioxanol (*S*,*S*,*S*)-**7** was obtained in good yield (77%) and excellent diastereo- and enantiomeric excess (*de* ≥ 96%, *ee* = 98%). The relative and absolute configuration of the

newly generated stereocenters was confirmed by NOE measurements. Thus, it is possible to create two neighbouring quaternary stereogenic centers in this manner with virtually complete asymmetric induction.



Scheme 4. Synthesis of the trifluoromethylated acetonide-protected triol **7**. a) *t*BuLi, THF, –78 °C, then MeI, –100 °C; b) *t*BuLi, THF, –78 °C, then MeI, –100 °C; c) *t*BuLi, THF, –78 °C, then *n*-$C_6H_{13}Br$, –100 °C; d) O_3, CH_2Cl_2, –78 °C; e) 1.5 equiv. $TMSCF_3$, 0.07 equiv. TBAF, THF, 0 °C; after completion: 1.5 equiv. TBAF, 1 h.

In the case of α,α′-disubstituted dioxanones bearing two side chains of similar steric demand only low diastereoselectivities in nucleophilic trifluoromethylations were observed indicating a limitation of our method.

Conclusions

Based on α-alkylated 1,3-dioxanones **3**, which can be obtained in high enantiomeric excesses via the SAMP/RAMP hydrazone methodology, we have developed an efficient asymmetric synthesis of trifluoromethylated (*S*,*S*)- and (*R*,*R*)-1,3-dioxan-5-ols **4**, respectively (*de* ≥96%, *ee* = 92 to ≥98%). The trifluoromethylation was carried out by nucleophilic 1,2-addition of the CF_3 group, generated from $TMSCF_3$ and TBAF, to the carbonyl group of the ketone **3**. Deprotection of dioxanol **4e** under acidic conditions gave the corresponding trifluoromethylated 1,2,3-triol **5** in essentially enantiomerically pure form (*ee* = 95, 96%). Additionally, we succeeded in extending our methodology to trialkylated 5-(trifluoromethyl)dioxanols **7** to get a wider spectrum of products and demonstrating that two neighbouring quaternary stereocenters can be generated with this protocol.

Experimental Section

General Remarks: Reagents of commercial quality were used from freshly opened containers. All solvents were purified and dried by conventional methods prior to use. Tetrahydrofuran was freshly distilled under argon from sodium/lead alloy in the presence of benzophenone. *t*BuLi (15% in *n*-pentane or 23% in *n*-hexane) was purchased from Merck, Darmstadt and TBAF (1 M in tetrahydrofuran) was purchased from Sigma–Aldrich. Activation of Dowex 50 was accomplished with 5 M HCl; after stirring for 30 min the solid was washed with water up to neutrality. Reactions under argon were carried out using standard Schlenk techniques. Preparative column chromatography: silica gel 60, particle size 0.040–0.063 mm (230–240 mesh), Merck, Darmstadt. Analytical TLC: silica gel 60 F_{254} plates, Merck, Darmstadt. Enantiomeric excesses were determined by GC_{CSP} [column: Lipodex E (25 m × 0.25 mm ID, D_F 0.25 μm)] or Chirasil dex (25 m × 0.25 mm ID, D_F 0.25 μm). Optical rotation values were measured with a Perkin–Elmer P241 Polarimeter, solvents used were of Merck UVASOL quality. Elementary analyses were obtained with a Heraeus CHN-O-Rapid. Mass spectra were recorded with Varian MAT 212 (EI, 70 eV, 1 mA) spectrometer. IR spectra were obtained with a Perkin–Elmer FT/IR 1760 instrument. NMR spectra were recorded with either Varian VXR 300, Varian Gemini 300, Varian Inova 400 or Varian Unity 500 spectrometers. For ^1H and ^{13}C NMR spectra tetramethylsilane was used as internal standard; for ^{19}F NMR spectra trichlorofluoromethane was used as external standard. Due to the fact that the solid compounds almost melted at room temperature, melting points are not determined. Hydrazones (*R*)- and (*S*)-**2** were prepared from (*R*)-1-amino-2-(methoxymethyl)pyrrolidine [RAMP] or (*S*)-1-amino-2-(methoxymethyl)pyrrolidine [SAMP][17] and 2,2-dimethyl-1,3-dioxan-5-one (**1**) according to literature procedures.[10,11] The analytical and spectroscopic data of the monoalkylated ketones **3a**–**e** and the trialkylated ketone **6** were in agreement with those reported previously.[11,12,16]

General Procedure for the Preparation of Monoalkylated Ketones (GP 1): SAMP- or RAMP-hydrazone **2** (1.0 equiv.) was dissolved in anhydrous tetrahydrofuran (4–5 mL/mmol hydrazone) under argon atmosphere and *t*BuLi (1.2 equiv.) was added dropwise at –78 °C. After stirring for 4 h at this temperature, the lithiated hydrazone was cooled to –100 °C and the electrophile (1.1 equiv., neat) was added slowly. After 1 h of stirring, the mixture was warmed up to room temperature over 15 h. The mixture was quenched with pH 7 buffer solution and diluted with diethyl ether. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with pH 7 buffer solution and brine. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The obtained monoalkylated SAMP-hydrazone was dissolved in dichloromethane (4–5 mL/mmol hydrazone) and ozonolyzed at –78 °C. The reaction was performed for 10 to 20 min monitoring for completion by TLC. After concentration under reduced pressure the crude product was purified by flash chromatography to afford the monoalkylated ketones (*S*)- and (*R*)-**3a**–**e**.

General Procedure for the Preparation of Trifluoromethylated Alcohols 4 (Catalytic Amounts of TBAF) (GP 2): TBAF (0.05–0.1 equiv.) was added to a stirred solution of dioxanone **3** (1.0 equiv.) and $TMSCF_3$ (1.5 equiv.) in tetrahydrofuran (5–6 mL/mmol dioxanone) at 0 °C. The reaction mixture was warmed up to room temperature. After completion of the reaction (TLC monitoring) TBAF (1.5 equiv.) was added. The reaction mixture was stirred for 1 h and then quenched with water. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with water and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography.

General Procedure for the Preparation of Trifluoromethylated Alcohols 4 (Stoichiometric Amounts of TBAF) (GP 3): At 0 °C, TBAF (1.5 equiv.) was added to a solution of dioxanone **3** (1.0 equiv.) and $TMSCF_3$ (1.5 equiv.) in tetrahydrofuran (5–6 mL/mmol dioxanone). The mixture was warmed up to room temperature. After completion of the reaction (TLC monitoring), the reac-

tion mixture was quenched with water. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with water and brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography.

(*S*,*S*)-2,2,4-Trimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*S*,*S*)-4a]: As described in GP 2 dioxanone (*S*)-**3a** (0.140 g, 0.97 mmol) was trifluoromethylated with $TMSCF_3$ (0.22 mL, 1.48 mmol) in the presence of TBAF (0.05 mL, 0.05 mmol) in tetrahydrofuran (6 mL). After deprotection with TBAF (1.5 mL, 1.5 mmol), dioxanol (*S*,*S*)-**4a** was obtained after purification by flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless solid. Yield: 0.143 g (69%). R_t = 2.4 min (CP-Sil-8, 80–10–300). R_f = 0.15 (pentane/diethyl ether, 9:1). $[\alpha]_D^{23}$ = +10.6 (*c* = 1.02, $CHCl_3$). *de* ≥ 96%. *ee* ≥ 98%. IR ($CHCl_3$): $\tilde{\nu}$ = 3846 cm^{-1} (w), 3760 (w), 3414 (s), 3005 (s), 2951 (s), 2909 (s), 1463 (s), 1382 (vs), 1289 (vs), 1203 (vs), 1110 (vs), 1053 (w), 1024 (m), 991 (s), 968 (s), 931 (m), 904 (m), 844 (s), 783 (m), 733 (s), 635 (w), 584 (w), 520 (s), 484 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (dd, *J* = 1.1, 6.3 Hz, 3 H, $CHCH_3$), 1.45 [s, 3 H, $C(CH_3)(CH_3)$], 1.48 [s, 3 H, $C(CH_3)(CH_3)$], 2.96 (s, 1 H, O*H*), 3.77 (d, *J* = 12.1 Hz, 1 H, C*H*H′), 4.06 (d, *J* = 12.1 Hz, 1 H, CH*H*′), 4.22 (q, *J* = 6.3 Hz, 1 H, $CHCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1 ($CHCH_3$), 18.5, 28.7 [$C(CH_3)_2$], 63.8 (CH_2), 66.8 (*C*H), 70.5 (q, $^2J_{CF}$ = 26 Hz, CCF_3), 99.2 [$C(CH_3)_2$], 124.1 (q, $^1J_{CF}$ = 283 Hz, CF_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –77.2 ppm. MS (EI): *m*/*z* (%) = 199 (23, $M^+ - CH_3$), 103 (13), 73 (5), 61 (13), 59 (100). $C_8H_{13}F_3O_3$ (214.21): calcd. C 44.86, H 6.12, found C 44.67, H 6.22.

(*R*,*R*)-2,2,4-Trimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*R*,*R*)-4a]: As described in GP 2 dioxanone (*R*)-**3a** (0.215 g, 1.49 mmol) was trifluoromethylated with $TMSCF_3$ (0.33 mL, 2.23 mmol) in the presence of TBAF (0.07 mL, 0.07 mmol) in tetrahydrofuran (9 mL). After deprotection with TBAF (2.2 mL, 2.2 mmol), dioxanol (*R*,*R*)-**4a** was afforded after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless solid. Yield: 0.188 g (59%). R_t = 2.4 min (CP-Sil-8, 80–10–300). R_f = 0.15 (pentane/diethyl ether, 9:1). $[\alpha]_D^{25}$ = –12.9 (*c* = 1.02, $CHCl_3$). *de* ≥ 96%. *ee* ≥ 98%. The spectroscopic data were in accordance with those of the enantiomer (*S*,*S*)-**4a**.

(*S*,*S*)-4-Ethyl-2,2-dimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*S*,*S*)-4b]: As described in GP 3 dioxanone (*S*)-**4b** (0.113 g, 0.71 mmol) was trifluoromethylated with $TMSCF_3$ (0.16 mL, 1.1 mmol) in the presence of TBAF (1.05 mL, 1.05 mmol) in tetrahydrofuran (3.5 mL). Dioxanol (*S*,*S*)-**3b** was obtained after flash chromatography (SiO_2, pentane/diethyl ether, 4:1) as a colorless solid. Yield: 0.140 g (86%). R_t = 3.9 min (CP-Sil-8, 60–10–300). R_f = 0.22 (pentane/diethyl ether, 9:1). $[\alpha]_D^{23}$ = –14.5 (*c* = 1.03, $CHCl_3$). *de* ≥ 96%, *ee* = 93%. IR (film): $\tilde{\nu}$ = 3457 cm^{-1} (s), 2990 (s), 2887 (m), 1791 (w), 1464 (m), 1382 (s), 1305 (w), 1199 (vs), 1157 (vs), 1113 (s), 1073 (w), 981 (s), 929 (m), 870 (s), 822 (w), 786 (m), 733 (m), 647 (w), 593 (w), 525 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3), 1.45 [s, 6 H, $C(CH_3)_2$], 1.64 (m, 2 H, CH_2CH_3), 3.02 (s, 1 H, O*H*), 3.73 (dd, *J* = 0.7, 12.1 Hz, 1 H, C*H*H′O), 3.91 (dd, *J* = 4.4, 8.4 Hz, 1 H, C*H*O), 4.04 (d, *J* = 12.1 Hz, 1 H, CH*H*′O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7 (CH_2CH_3), 18.9, 28.3 [$C(CH_3)_2$], 21.7 (CH_2CH_3), 64.2 (CH_2O), 71.3 (q, $^2J_{CF}$ = 27 Hz, CCF_3), 72.2 (*C*H), 99.7 [$C(CH_3)_2$], 124.5 (q, $^1J_{CF}$ = 284 Hz, CF_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –77.1 ppm. MS (EI): *m*/*z* (%) = 213 (11, $M^+ - CH_3$), 117 (7), 61 (13), 60 (100). $C_9H_{15}F_3O_3$ (228.24): calcd. C 47.36, H 6.64, found C 47.32, H 6.89.

(*R*,*R*)-4-Ethyl-2,2-dimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*R*,*R*)-4b]: As described in GP 3 dioxanone (*R*)-**2b** (0.093 g, 0.59 mmol) was trifluoromethylated with $TMSCF_3$ (0.14 mL, 0.95 mmol) in the presence of TBAF (0.98 mL, 0.98 mmol) in tetrahydrofuran (4 mL). Dioxanol (*R*,*R*)-**4b** was obtained after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless solid. Yield: 0.070 g (52%). R_t = 3.8 min (CP-Sil-8, 60–10–300). R_f = 0.22 (pentane/diethyl ether, 9:1). $[\alpha]_D^{23}$ = +14.2 (*c* = 0.99, $CHCl_3$). *de* ≥ 96%, *ee* = 93%. The spectroscopic data were in accordance with those of the enantiomer (*S*,*S*)-**4b**.

(*S*,*S*)-4-Isopropyl-2,2-dimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*S*,*S*)-4c]: As described in GP 2 dioxanone (*S*)-**4c** (0.256 g, 1.5 mmol) was trifluoromethylated with $TMSCF_3$ (0.33 mL, 2.23 mmol) in the presence of TBAF (0.15 mL, 0.15 mmol) in tetrahydrofuran (7.5 mL). After deprotection with TBAF (2.3 mL, 2.3 mmol), dioxanol (*S*,*S*)-**4c** was obtained after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless solid. Yield: 0.270 g (75%). R_t = 4.3 min (CP-Sil-8, 60–10–300). R_f = 0.40 (pentane/diethyl ether, 9:1). $[\alpha]_D^{25}$ = –4.5 (*c* = 0.53, $CHCl_3$). *de* ≥ 96%, *ee* = 92%. IR (film): $\tilde{\nu}$ = 3457 cm^{-1} (s), 2990 (s), 2887 (m), 1791 (w), 1464 (m), 1382 (s), 1305 (w), 1199 (vs), 1157 (vs), 1113 (s), 1073 (w), 981 (s), 929 (m), 870 (m), 822 (w), 786 (m), 733 (m), 647 (w), 593 (w), 525 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 7.1 Hz, 3 H, $CHCH_3$), 1.04 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 1.44 [s, 3 H, $C(CH_3)(CH_3)$], 1.46 [s, 3 H, $C(CH_3)(CH_3)$], 2.10 [m, 1 H, $CH(CH_3)_2$], 2.97 (s, 1 H, O*H*), 3.68 (d, *J* = 11.5 Hz, 1 H, C*H*H′O), 3.86 (d, *J* = 2.2 Hz, 1 H, C*H*O), 3.98 (d, *J* = 11.8 Hz, 1 H, CH*H*′O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 21.2 [$CH(CH_3)_2$], 18.4, 28.5 [$C(CH_3)_2$], 65.1 (CH_2), 72.2 (q, *J* = 27 Hz, CCF_3), 73.6 (*C*HO), 99.5 [$C(CH_3)_2$], 124.4 (q, *J* = 283 Hz, CF_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –77.2 ppm. MS (EI): *m*/*z* (%) = 243 (5), 227 (6, $M^+ - CH_3$), 199 (6), 149 (8), 131 (10), 73 (11), 61 (6), 59 (100), 56 (6). $C_{10}H_{17}F_3O_3$ (242.27): calcd. C 49.57, H 7.09, found C 49.27, H 7.20.

(*R*,*R*)-4-Isopropyl-2,2-dimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*R*,*R*)-4c]: As described in GP 3 dioxanone (*R*)-**3b** (0.102 g, 0.59 mmol) was trifluoromethylated with $TMSCF_3$ (0.13 mL, 0.88 mmol) in the presence of TBAF (0.89 mL, 0.89 mmol) in tetrahydrofuran (4 mL). Dioxanol (*R*,*R*)-**4c** was obtained after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless solid. Yield: 0.104 g (73%). R_t = 4.3 min (CP-Sil-8, 60–10–300). R_f = 0.40 (pentane/diethyl ether, 9:1). $[\alpha]_D^{25}$ = +4.2 (*c* = 0.17, $CHCl_3$). *de* ≥ 96%, *ee* = 93%. The spectroscopic data were in accordance with those of the enantiomer (*S*,*S*)-**4c**.

(*S*,*S*)-4-Butyl-2,2-dimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*S*,*S*)-4d]: As described in GP 3 dioxanone (*S*)-**3d** (0.185 g, 0.99 mmol) was trifluoromethylated with $TMSCF_3$ (0.20 mL, 1.35 mmol) in the presence of TBAF (1.5 mL, 1.5 mmol) in tetrahydrofuran (5 mL). Dioxanol (*S*,*S*)-**4d** was obtained after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless solid. Yield: 0.162 g (64%). R_t = 4.6 min (CP-Sil-8, 80–10–300). R_f = 0.38 (pentane/diethyl ether, 4:1). $[\alpha]_D^{23}$ = –16.4 (*c* = 0.97, $CHCl_3$). *de* ≥ 96%, *ee* = 94%. IR ($CHCl_3$): $\tilde{\nu}$ = 3582 cm^{-1} (s), 3470 (s), 2961 (vs), 2872 (vs), 1465 (s), 1382 (s), 1294 (s), 1265 (s),1198 (vs), 1118 (vs), 1064 (s), 1016 (m), 984 (s), 945 (s), 909 (m), 861 (s), 821 (m), 792 (m), 751 (m), 736 (m), 669 (w), 646 (m), 594 (m), 524 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.9 Hz, 3 H, CH_2CH_3), 1.19–1.70 (m, 6 H, $CH_2CH_2CH_2$), 1.44 [s, 3 H, $C(CH_3)(CH_3)$], 1.45 [s, 3 H, $C(CH_3)(CH_3)$], 2.93 (br.s, 1 H, O*H*), 3.74 (d, *J* = 12.1 Hz, 1 H, C*H*H′), 4.00 (m, 1 H, $CHCH_2$), 4.05 (d, *J* = 12.1 Hz, 1 H, CH*H*′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH_2CH_3), 18.8, 28.3 [$C(CH_3)$], 22.4, 27.1, 28.0 [$(CH_2)_3$], 64.1 (CH_2O), 70.5 (*C*H), 71.2 (q, $^2J_{CF}$ = 26 Hz, CCF_3), 99.4 [$C(CH_3)_2$], 124.3 (q, $^1J_{CF}$ = 284 Hz, CF_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$):

δ = –77.0 ppm. MS (EI): *m*/*z* (%) = 241 (6, $M^+ - CH_3$), 226 (6), 181 (5), 173 (19), 145 (11), 130 (10), 115 (7), 113 (5), 99 (7), 98 (5), 97 (10), 85 (24), 73 (8), 69 (16), 61 (7), 59 (100), 57 (12), 55 (8). $C_{11}H_{19}F_3O_3$ (256.30): calcd. C 51.55, H 7.49, found C 51.17, H 7.34.

(*R*,*R*)-4-Butyl-2,2-dimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*R*,*R*)-4d]: As described in GP 3 dioxanone (*R*)-**3d** (0.158 g, 0.85 mmol) was trifluoromethylated with $TMSCF_3$ (0.19 mL, 1.3 mmol) in tetrahydrofuran (5 mL). Dioxanol (*R*,*R*)-**4d** was obtained after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless solid. Yield: 0.159 g (73%). R_t = 4.5 min (CP-Sil-8, 80–10–300). R_f = 0.17 (pentane/diethyl ether, 9:1). $[\alpha]_D^{24}$ = +17.0 (*c* = 1.05, $CHCl_3$). *de* ≥ 96%, *ee* = 94%. The spectroscopic data were in accordance with those of the enantiomer (*S*,*S*)-**4d**.

(*S*,*S*)-4-Hexyl-2,2-dimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*S*,*S*)-4e]: As described in GP 3 dioxanone (*S*)-**3e** (0.148 g, 0.69 mmol) was trifluoromethylated with $TMSCF_3$ (0.15 mL, 1.01 mmol) in the presence of TBAF (1.05 mL, 1.05 mmol) in tetrahydrofuran (3.5 mL). Dioxanol (*S*,*S*)-**4e** was obtained after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless solid. Yield: 0.184 g (94%). R_t = 6.9 min (CP-Sil-8, 80–10–300). R_f = 0.21 (pentane/diethyl ether, 9:1). $[\alpha]_D^{24}$ = –17.6 (*c* = 1.04, $CHCl_3$). *de* ≥ 96%, *ee* = 95%. IR ($CHCl_3$): $\tilde{\nu}$ = 3877 cm^{-1} (w), 3723 (w), 3524 (w), 3496 (w), 3413 (w), 3335 (w), 2929 (vs), 2862 (s), 1463 (m), 1380 (s), 1299 (w), 1267 (w), 1200 (vs), 1154 (s), 1116 (m), 1062 (w), 985 (s), 936 (m), 890 (m), 854 (m), 760 (w), 735 (m), 643 (m), 593 (m), 525 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.8 Hz, 3 H, C*H*$_3$), 1.20–1.71 [m, 10 H, (C*H*$_2$)$_5$], 1.44 [s, 3 H, C(C*H*$_3$)], 1.45 [s, 3 H, C(C*H*$_3$)], 2.95 (br.s, 1 H, O*H*), 3.74 (d, *J* = 12.1 Hz, 1 H, C*H*H′), 4.00 (m, 1 H, C*H*CH$_2$), 4.04 (d, *J* = 12.1 Hz, 1 H, CH*H*′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH$_2$*C*H$_3$), 18.9, 28.3 [C(*C*H$_3$)$_2$], 22.6, 25.0, 28.4, 29.0, 31.8 [(*C*H$_2$)$_5$], 64.2 (*C*H$_2$O), 70.6 (*C*H), 71.3 (q, $^2J_{CF}$ = 26 Hz, *C*CF$_3$), 99.6 [*C*(CH$_3$)$_2$], 124.5 (q, $^1J_{CF}$ = 284 Hz, *C*F$_3$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –77.0 ppm. MS (EI): *m*/*z* (%) = 285 (52), 269 (20, $M^+ - CH_3$), 209 (13), 173 (13), 149 (5), 97 (11), 59 (100), 56 (13). $C_{13}H_{23}F_3O_3$ (284.36): calcd. C 54.91, H 8.17, found C 54.65, H 7.91.

(*R*,*R*)-4-Hexyl-2,2-dimethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*R*,*R*)-4e]: As described in GP 3 dioxanone (*R*)-**3e** (0.110 g, 0.51 mmol) was trifluoromethylated with $TMSCF_3$ (0.11 mL, 0.74 mmol) in tetrahydrofuran (3.5 mL). Dioxanole (*R*,*R*)-**4e** could be obtained after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless oil. Yield: 0.141 g (97%). R_t = 6.9 min (CP-Sil-8, 80–10–300). R_f = 0.21 (pentane/diethyl ether, 9:1). $[\alpha]_D^{24}$ = +17.1 (*c* = 1.01, $CHCl_3$). *de* ≥ 96%, *ee* = 96%. The spectroscopic data were in accordance with those of the enantiomer (*S*,*S*)-**4e**.

(*S*,*S*)-2-(Trifluoromethyl)nonane-1,2,3-triol [(*S*,*S*)-5]: Dioxanol (*S*,*S*)-**4e** (0.107 g, 0.38 mmol) was dissolved in ethanol (0.3 mL). After addition of freshly activated Dowex 50, the reaction mixture was stirred up to completion of the reaction (tlc control). The solid was removed by filtration and washed with diethyl ether and the organic layer was dried with $MgSO_4$ and concentrated in vacuo. The product was purified by flash chromatography (SiO_2, pentane/diethyl ether, 4:1, then diethyl ether) and triol (*S*,*S*)-**5** was obtained as a colorless oil. Yield: 0.084 g (90%). R_f = 0.84 (diethyl ether). $[\alpha]_D^{26}$ = –22.6 (*c* = 1.00, CH_3OH). *de* = 90%, *ee* = 95%. IR ($CHCl_3$): $\tilde{\nu}$ = 3405 cm^{-1} (vs), 2958 (vs), 2930 (vs), 2860 (s), 1636 (w), 1466 (m), 1405 (w), 1380 (w), 1243 (m), 1176 (vs), 1077 (s), 951 (w), 723 (w), 689 (w), 648 (w) cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 0.87 (m, 3 H, C*H*3), 1.20–1.60 [m, 10 H, (C*H*$_2$)$_5$], 3.55 (dd, *J* = 5.5, 11.5 Hz, 1 H, C*H*H′OH), 3.64 (m, 1 H, C*H*OH), 3.69 (dd, *J* = 5.5, 11.5 Hz, 1 H, CH*H*′O), 4.72 (d, *J* = 7.4 Hz, 1 H, CHO*H*), 4.82 (t, *J* = 5.8 Hz, 1 H, CHH′O*H*), 5.47 [s, 1 H, C(CF$_3$)O*H*] ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 14.4 (*C*H$_3$), 22.5, 26.5, 29.1, 30.9, 31.8 [(*C*H$_2$)$_5$], 60.7 (*C*H$_2$OH), 70.5 (*C*HOH), 76.6 (q, $^2J_{CF}$ = 23 Hz, *C*OH), 127.0 (q, $^1J_{CF}$ = 290 Hz, *C*F$_3$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –72.80 ppm. MS (EI): *m*/*z* (%b.p.) = 166 (5), 115 (49), 112 (11), 110 (5), 109 (5), 98 (6), 97 (74), 70 (5), 69 (15), 57 (8), 56 (9), 55 (100). MS (CI): *m*/*z* (%) = 245 (35, M^++1), 243 (15), 227 (29), 225 (8), 210 (10), 209 (100), 207 (6), 192 (5), 191 (48), 189 (7), 157 (5), 153 (5), 149 (30), 139 (7), 135 (7), 115 (23), 97 (24), 83 (6), 69 (5). $C_{10}H_{19}F_3O_3$ (244.25): calcd. C 49.17, H 7.84, found C 49.42, H 7.56.

(*R*,*R*)-2-(Trifluoromethyl)nonane-1,2,3-triol [(*R*,*R*)-5]: Dioxanol (*R*,*R*)-**4e** (0.203 g, 0.71 mmol) was dissolved in ethanol (0.6 mL). After addition of freshly activated Dowex 50, the reaction mixture was stirred up to completion of the reaction. The solid was removed by filtration and washed with diethyl ether and the organic liquid was dried with $MgSO_4$ and concentrated in vacuo. The product was purified by flash chromatography (SiO_2, pentane/diethyl ether, 4:1, then diethyl ether) and triol (*R*,*R*)-**5** was furnished as a colorless oil. Yield: 0.150 g (86). R_f = 0.84 (diethyl ether). $[\alpha]_D^{26}$ = +25.4 (*c* = 0.67, CH_3OH). *de* ≥ 96%, *ee* = 96%. The spectroscopic data were in accordance with those of the enantiomer (*S*,*S*)-**5**.

(*S*,*S*,*S*)-4-Hexyl-2,2,4,6-tetramethyl-5-(trifluoromethyl)-1,3-dioxan-5-ol [(*S*,*S*,*S*)-7]: According to **GP 2** trisalkylated dioxanone (*S*,*S*)-**6** (0.070 g, 0.29 mmol) was dissolved in tetrahydrofuran (2 mL) and trifluoromethylated with $TMSCF_3$ (0.10 mL, 0.68 mmol) in the presence of TBAF (0.02 mL, 0.02 mmol). After deprotection with TBAF (0.44 mL, 0.44 mmol), dioxanol (*S*,*R*,*S*)-**7** was obtained after flash chromatography (SiO_2, pentane/diethyl ether, 9:1) as a colorless oil. Yield: 0.086 g (77%). R_t = 6.5 min (CP-Sil-8, 100–10–300). R_f = 0.51 (pentane/diethyl ether, 9:1). $[\alpha]_D^{24}$ = –29.3 (*c* = 0.98, $CHCl_3$). *de* ≥ 96%, *ee* = 92%. IR ($CHCl_3$): $\tilde{\nu}$ = 3981 cm^{-1} (w), 3849 (w), 3830 (w), 3731 (w), 3652 (w), 3566 (s), 3490 (w), 3457 (w), 3348 (w), 3199 (w), 3146 (w), 2998 (s), 2959 (vs), 2859 (s), 2734 (w), 1463 (s), 1382 (s), 1323 (w), 1251 (s), 1196 (vs), 1092 (m), 1025 (s), 974 (w), 947 (m), 905 (m), 884 (m), 831 (m), 742 (m), 714 (m), 614 (w), 533 (w), 473 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.9 Hz, 3 H, CH$_2$C*H*$_3$), 1.25 (m, 3 H, CHC*H*$_3$), 1.28–1.56 [kB, 17 H, C(C*H*$_3$)$_2$, CC*H*$_3$, CH$_2$(C*H*$_2$)$_4$CH$_3$], 1.96 [m, 2 H, C*H*$_2$(CH$_2$)$_4$CH$_3$], 2.84 (s, 1 H, O*H*), 4.40 (q, *J* = 6.3 Hz, 1 H, C*H*CF$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (CH$_2$*C*H$_3$), 15.8 (CH*C*H$_3$), 22.6, 22.9 [(*C*H$_2$)$_2$CH$_3$], 23.0, 23.3, 31.6 [C*C*H$_3$, C(*C*H$_3$)$_2$], 29.8, 31.8 [CCH$_2$(*C*H$_2$)$_2$], 35.4 (C*C*H$_2$), 64.4 (*C*HCH$_3$), 74.7 (q, $^2J_{CF}$ = 26 Hz, *C*CF$_3$), 79.8 (*C*CH$_3$), 98.7 [C(*C*H$_3$)$_2$], 124.9 (q, $^1J_{CF}$ = 285 Hz, *C*F$_3$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –68.8 ppm. MS (EI): *m*/*z* (%) = 297 (13, $M^+ - CH_3$), 237 (5), 227 (13), 210 (7), 163 (7), 130 (6), 129 (66), 111 (15), 87 (5), 69 (31), 61 (20), 59 (100), 58 (9), 57 (8), 55 (15), 45 (5). $C_{15}H_{27}F_3O_3$ (312.27): calcd. C 57.68, H 8.71, found C 57.64, H 8.78.

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