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Regio- and diastereoselectivity in $TiCl_4$-promoted reduction of 2-aryl-substituted *cis*-4-methyl-5-trifluoromethyl-1,3-dioxolanes

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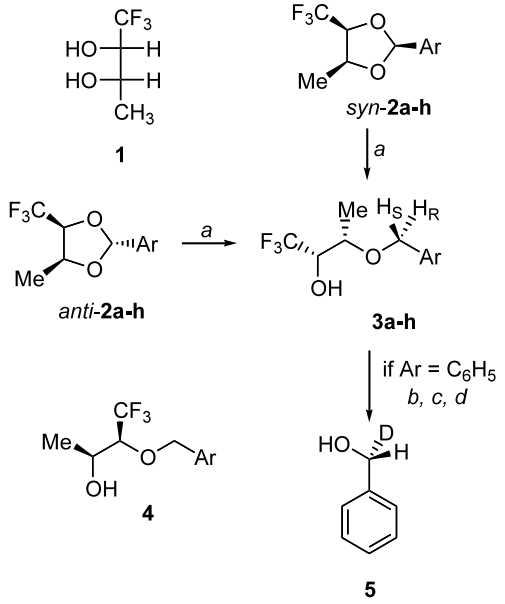
Abstract—$TiCl_4$-mediated reduction of both *syn*- and *anti*-(4*S*,5*S*)-2-aryl-4-methyl-5-trifluoromethyl-1,3-dioxolanes with Et_3SiD furnished monodeuterated hydroxy ethers resulting from the same regio- and stereoselective C–O bond cleavage (yields >80%; 82–92% de). Deuteride addition to the benzylidene acetal and removal of the alkyl moiety from the reaction product gave (*R*)-(α-^{2}H)benzyl alcohol (90% ee), thus suggesting a new route to chiral 1-deuteriobenzyl alcohols. A mechanistic rationale is proposed and supported by theoretical calculations.

1. Introduction

The exploitation of cyclic acetals as chiral templates that temporarily modify the environment and reactivity of carbonyl groups continues to attract the attention of organic chemists.[1] Main interests are the applications of Lewis acid-promoted nucleophilic substitution at the acetal carbon to asymmetric synthesis[1b] as well as the relationship between mechanism and stereoselectivity.[2] A number of di- and trisubstituted 1,3-dioxolanes, 1,3-dioxanes, and 1,3-dioxepanes have been examined as chiral templates.[1,2a] The recent synthesis of the four stereoisomers of 1,1,1-trifluorobutane-2,3-diol in enantiomeric pure form[3] prompted us to examine them as auxiliaries for stereoselective nucleophilic additions to aldehydes via acetal intermediates. We report herein the results of $TiCl_4$-mediated reductive ring cleavage of dioxolane acetals derived from (2*S*,3*S*)-1,1,1-trifluorobutane-2,3-diol **1** with substituted benzaldehydes. A mechanistic interpretation is also suggested.

2. $TiCl_4$-mediated reduction of dioxolanes

The diastereomeric trisubstituted 1,3-dioxolanes *syn*- and *anti*-**2a** were prepared by reaction of benzaldehyde with **1** (95% ee) and a catalytic amount of *p*-TsOH in toluene (Scheme 1). The relative configurations of *syn*- and *anti*-**2a** were proved by ^{1}H NOESY experiments. When compound *syn*-**2a** was treated with $TiCl_4$ and



Scheme 1. *Reagents and conditions*: (a) $TiCl_4$, $Et_3SiH(D)$, CH_2Cl_2, −78°C; (b) Swern oxidation; (c) NaH, THF, reflux; (d) TEA, diphenyl phosphoroazidate (DPPA); 1 M HCl, reflux. See Table 1 for aryl residues.

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Et_3SiH in CH_2Cl_2 at −78°C the monobenzyl ether **3a** was produced as the only reaction product (isolated yield: 95%).

Compound **3a** was identified by comparison with an authentic sample obtained as an intermediate in the synthesis of **1**.[3] The formation of the regioisomer **4** (Ar = C_6H_5) was not detected by GC analysis of the reaction mixture.

The $TiCl_4$-catalyzed ring opening of *syn*-**2a** in the presence of Et_3SiD (isotopic purity >99% D)[4] gave the expected reaction product which was shown to be stereospecifically monodeuterated at the benzylic position, i.e. **3a** (H_R = D). In fact, the ^1H NMR spectrum exhibited two broad singlets at δ 4.52 and 4.67 having an intensity ratio 15.5:1, instead of the typical AB pattern due to the diastereotopic benzylic protons. In conjunction with this, the *R* configuration of the O-CHD-C_6H_5 group was deduced from chemical correlation (Scheme 1) of the monodeuterated hydroxy ether with (*R*)-(α-^2H)benzyl alcohol (**5**, 90% ee) via Swern oxidation,[5] subsequent haloform reaction,[6] and Curtius rearrangement.[7] The absolute configuration and ee of **5** were determined by comparison with an authentic sample of (*S*)-(α-^2H)benzyl alcohol[8] through ^1H NMR analysis of MTPA esters.[9] The ee of the benzyl alcohol was in accord with the ee of **1**[3] and the observed diastereoselectivity of the C–O bond cleavage of *syn*-**2a**.

The dioxolane *anti*-**2a** afforded compound **3a** (H_R = D) under the same reaction conditions ($TiCl_4$ and Et_3SiD) as for its *syn*-isomer. A number of $TiCl_4$-promoted deuteride substitutions at the acetal carbon of **2b**–**h** prepared from different benzaldehydes were performed with both *syn*- and *anti*-isomers (Table 1).

Some features of these reactions are worthy of note: (i) isolated yields in benzyl ethers are generally good and reflect a regioselectivity of ca. 100% corresponding to C2–O1 bond cleavage in all dioxolanes; (ii) diastereoselectivity is also very high and independent of the relative configuration of the 2-substituted 1,3-dioxolanes.

3. Mechanistic hypotheses and theoretical calculations

A possible mechanistic rationale for our findings is outlined in Scheme 2 and is based on the following considerations. It is likely that the reduction of acetal carbon atoms occurs via oxocarbenium ions, as reported for Lewis acid-catalyzed ring opening of cyclic acetals.[10,11] Thus, the regioselectivity in the 1,3-dioxolane ring cleavage can be explained in terms of a stronger destabilizing effect exerted by the CF_3 group on those ions in which such an electron-withdrawing group is closer to the positive charge. In other words, the ring opening of an O1–$TiCl_4$ complex (*syn*- and *anti*-**IA** in Scheme 2) is expected to be preferred to one involving C2–O3 bond breaking in the O3–$TiCl_4$ complexes *syn*- and *anti*-**IB** (Scheme 2).

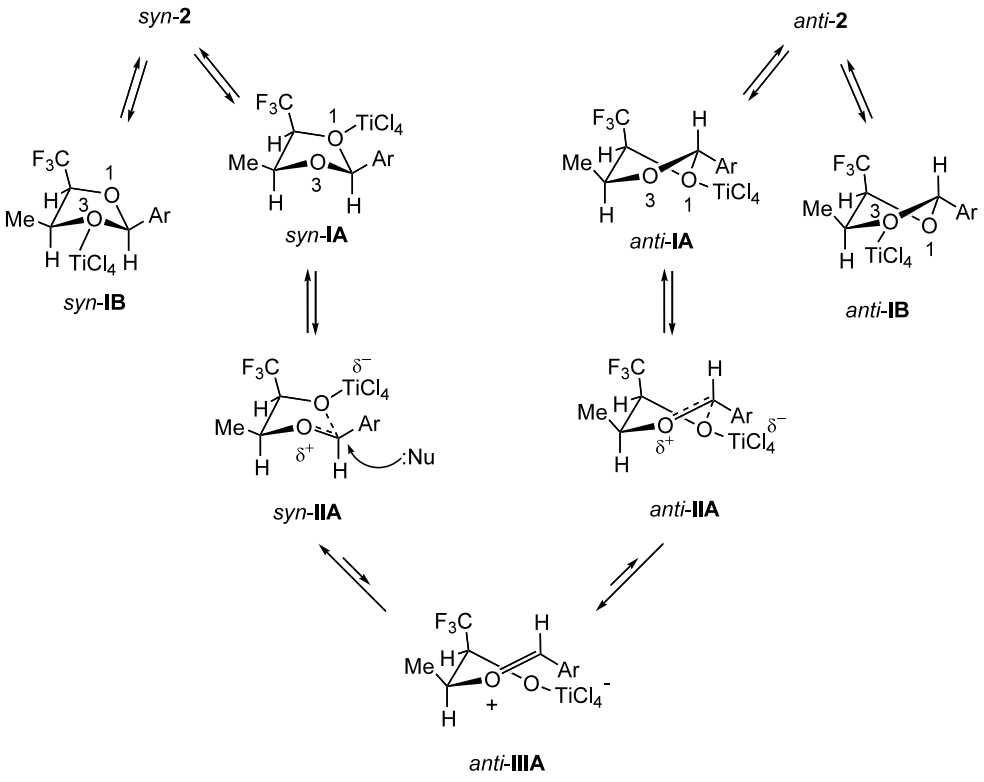
The fact that the same stereochemical outcome results from the deuteride substitution of O1 in both diastereomers *syn*-**2a**–**h** and *anti*-**2a**–**h** (Table 1) is consistent with a predominance of attack of Et_3SiD on the contact ion pair *syn*-**IIA**. As shown in Scheme 2, a fast conversion of *anti*-**IIA** into *syn*-**IIA** should occur, involving rotation about the C4–C3 bond in the external ion pair *anti*-**IIIA**, in competition with a much slower nucleophilic substitution reaction. Analogously *syn*-**IIA** would produce *anti*-**IA** giving rise to an equilibrium between diastereomeric Lewis acid complexes, largely displaced toward *syn*-**IA** and the corresponding contact ion pair.

The intrinsic instability and the dual behavior (isomerization versus nucleophilic substitution) of the contact ion pairs generated by the complexes *anti*-**IA** might explain the significantly lower yields and *R*/*S* ratios observed for the reaction products **3** of *anti*-1,3-dioxolanes (Table 1). The displacement of the configurational equilibrium toward *syn*-species implies a marked difference in energy between the *anti* and *syn* O1–$TiCl_4$ complexes **IA** (not necessarily between *anti*- and *syn*-**2**). To validate this assumption, theoretical calculation of energies and geometries of *syn*-**2a** and *anti*-**2a**, and their $TiCl_4$ complexes, *syn*-**IA** (Ar = C_6H_5) and *anti*-**IA** (Ar = C_6H_5), were performed.

Table 1. $TiCl_4$-mediated reaction of compounds **2** (*syn* and *anti*) with Et_3SiD to give compounds **3**

1,3-Dioxolane (*syn*-**2** or *anti*-**2**)		Compound **3** (α-^2H)			
		Isolated yields (%)		Diastereoisomeric ratio[a] *R*-Cα:*S*-Cα	
Entry	Ar =	From *syn*	From *anti*	From *syn*	From *anti*
a	C_6H_5	95	75	94:6	93:7
b	*p*-Me-C_6H_4	93	81	93:7	92:8
c	2-Naphthyl	84	84	96:4	94:6
d	*p*-Br-C_6H_4	80	64	95:5	93:7
e	*m*-NO_2-C_6H_4	93	63	91:9	88:12
f	*p*-NO_2-C_6H_4	92	71	92:8	87:13
g	*m*-OMe-C_6H_4	89	73	91:9	89:11
h	*p*-OMe-C_6H_4	84	67	91:9	88:12

[a] Determined by integration of the two benzylic (C_α) proton signals in the ^1H NMR spectra on the assumption, based on the configuration of **5**, that the upfield singlet was due to H_S (cf. **3**) and the isotopic abundance of the examined compound was >99% D (cf. Ref. 4).



Scheme 2. Proposed mechanism of configurational isomerization at C-2 of 1,3-dioxolanes via $TiCl_4$ complexes.

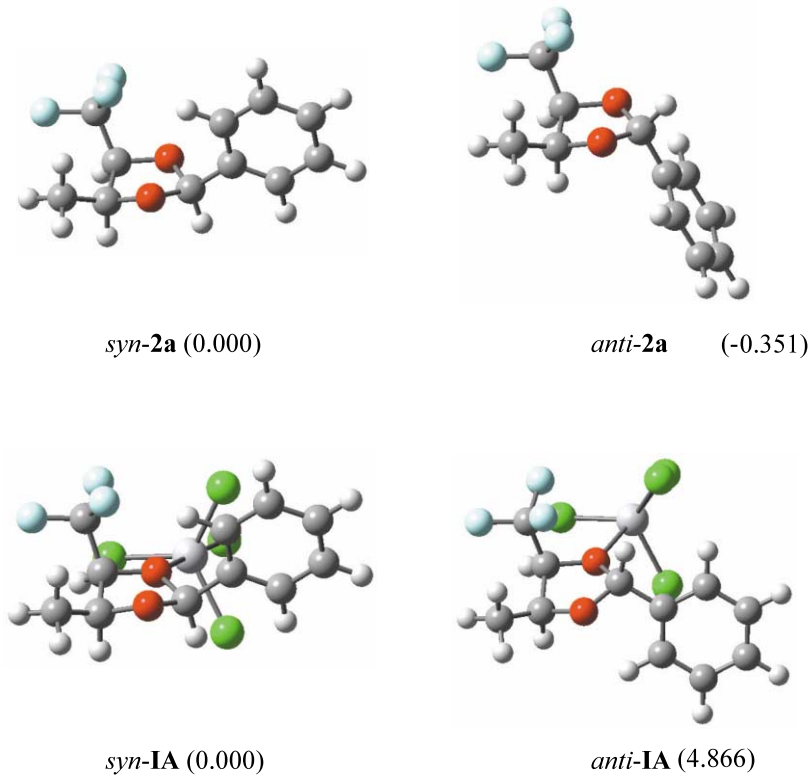


Figure 1. Calculated geometries and relative energies (in parentheses, in kcal mol^{-1}) of global minima of diastereomeric benzaldehyde acetals (above) and their $TiCl_4$ complexes (below). Structures *syn*-**IA** and *anti*-**IA** represent O1–$TiCl_4$ complexes of compounds *syn*-**2a** and *anti*-**2a**. See Table 2 for bond lengths.

Table 2. Calculated bond lengths (Å) of *syn* and *anti*-**2a** and their complexes with $TiCl_4$ at the LANL2DZ level

Compound[a]	C2–O1 (Δr)[b]	C2–O3 (Δr)[b]
syn-**2a**	1.505	1.448
anti-**2a**	1.486	1.451
syn-**IA**	1.638 (0.133)	1.412 (−0.036)
anti-**IA**	1.563 (0.077)	1.444 (−0.007)

[a] Structures in Fig. 1.

[b] Δr values reported in parentheses indicate lengthening ($\Delta r > 0$) or shortening ($\Delta r < 0$) of the bonds with respect to the uncomplexed dioxolanes.

The structures of the global minima of the configurational isomers of **2a** are reported in Fig. 1. For both of them the $TiCl_4$ molecule was then placed in proximity of O1 and the geometries of the two complexes were optimized at the DFT level using the B3LYP functional and the LANL2DZ basis set. All the calculations were carried out using the Gaussian G98 package[12] (see Section 5). The complex resulting from the *syn*-isomer was found to be thermodynamically more stable by ca. 5 kcal/mol. Inspection of Fig. 1 reveals that in this complex the aromatic ring substantially maintains the 'perpendicular' orientation relative to the heterocyclic ring as in the uncomplexed *syn*-dioxolane.

In contrast, the attachment of the $TiCl_4$ molecule to O1 of the *anti*-isomer causes rotation of the phenyl group by ca. −75° from the 'parallel' orientation, which was found to be the favored one in the *anti*-dioxolanes (compare *anti*-**2a** and complex *anti*-**IA** in Fig. 1). In addition, as a consequence of the modification in the dioxolane conformation, the hydrogen atom at C2 becomes *quasi*-axial giving rise to a steric interaction with the CF_3 group. A rotation about the C4–O3 bond via intermediate ion pair (Scheme 2) should relieve the above steric interactions (compare *syn*-**IA** and *anti*-**IA** in Fig. 1).

It can be noted that the Lewis acid complexation causes lengthening of the bond between C2 and the complexed oxygen atom, whilst the other C–O bond shortens (Table 2). This fact can be interpreted in terms of anomeric effect,[13] as suggested by Yamamoto for 1,3-dioxanes.[14] The C–O bond lengthening is particularly marked in complex *syn*-**A** which thus appears to be the most likely candidate on the basis of relative population/reactivity for the nucleophilic substitution reaction, as shown in Scheme 2.

4. Conclusions

Our findings indicate that the CF_3 group as a substituent of 2-aryl-1,3-dioxolanes determines the regioselectivity of the $TiCl_4/Et_3SiH$ ring opening at the level of the benzylic carbon. The reductive cleavage of the C–O bond closer to the electron withdrawing group occurs to the extent of practically 100%.[15] Interestingly, the stereochemical outcome of the deuteride substitution of the oxygen of the acetal carbon is the same for both the C2 epimers of 1,3-dioxolanes (Table 1). This feature, which eliminates the chromatographic separation of diastereomeric acetals **2**, together with the availability of enantiomerically pure (*R*,*R*)- and (*S*,*S*)-1,1,1-trifluorobutane-2,3-diols **1**[3] makes the procedure summarized in Scheme 1 an alternative route to chiral benzylic alcohols with good enantiomeric excess.[16] Work is in progress to explore mechanistic aspects and synthetic potentialities of nucleophilic substitution at acetal carbons having the CF_3 group β-positioned with respect to the ethereal oxygen.

5. Experimental

5.1. General

TLC was performed on silica gel F254 precoated aluminum sheets (0.2 mm layer, Merck, Darmstadt, Germany); components were detected by spraying with ceric sulphate ammonium molybdate solution, followed by heating to ca. 150°C. Silica gel (Merck, 40–63 μm) was used for flash chromatography (FC). GC analyses were carried out on a DANI 3800 gas chromatograph (DANI, Monza, Italy) using a home made glass column (2 m× 2 mm i.d.) packed with 10% FFAP on Chromosorb W (60–80 mesh); GC parameters: injector, 220°C; detector (FID), 220°C; carrier, N_2 (30 ml/min); oven, isothermal analysis at 200°C. ^1H and ^{13}C NMR spectra were acquired at 400.132 and 100.613 MHz on a Bruker AVANCE 400 Spectrometer using a Xwin-NMR software package and at 300.133 and 75.47 on a Bruker AC 300 (Bruker, Karlsruhe, Germany) equipped with an ASPECT 3000 data system. Chemical shifts (δ) are given in ppm and were referenced to the signals of $CDCl_3$ (δ_H 7.25 and δ_C 77.00 ppm). ^{13}C NMR signals multiplicities were based on APT spectra. All reagents were of commercial quality or purified prior to use by standard methods.

5.2. General procedure for the synthesis of 2-aryl-4-methyl-5-trifluoromethyl-1,3-dioxolanes, *syn*- and *anti*-2

A solution of diol **1**, arylaldehyde (1.2 equiv.) and a catalytic amount of *p*-toluenesulfonic acid in dry toluene (0.3 mmol of **1**/ml) was heated under reflux with removal of water by means of a Dean–Stark apparatus until disappearance of the starting diol (GC). The solution was diluted with ethyl acetate, washed with saturated hydrogencarbonate, 10% sodium hydrogensulfite solution and saturated NaCl. The organic layer was separated and dried (Na_2SO_4). The diastereomeric dioxolanes *syn* and *anti* **2** were separated by flash column chromatography.

5.2.1. (2*S*,4*S*,5*S*)-4-Methyl-2-phenyl-5-trifluoromethyl-1,3-dioxolane, *syn*-2a and (2*R*,4*S*,5*S*)-4-methyl-2-phenyl-5-trifluoromethyl-1,3-dioxolane, *anti*-2a. Obtained from **1** and benzaldehyde in 55 and 30% yield, respectively; eluent for FC: EtOAc/hexane, 1/12.

syn-**2a**: Pale yellow liquid. GC t_R 1.9 min. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.60$ (dq, $J_{HH} = 6.6$ Hz, $J_{HF} =$

1.8 Hz, 3H, Me), 4.37 (dq, $J_{HH}=J_{HF}=6.6$ Hz, 1H, H-5), 4.46 (dqq, $J_{HH}=6.6$ Hz, $J_{HF}=1.7$ Hz, 1H, H-4), 5.86 (s, 1H, H-2), 7.41–7.57 (m, 5H, aromatic H). Associations between H-2 and H-4/H-5 in the NOESY spectrum. ^{13}C NMR (100 MHz): $\delta=13.47$ (Me), 74.68 (C-4), 75.22 (q, $^2J_{CF}=31$ Hz, C-5), 104.43 (C-2), 123.60 (q, $^1J_{CF}=282$ Hz, CF_3), 127.04, 128.45, 129.94 and 135.43 (aromatic C); $[\alpha]_D$ +25.4 (*c* 1.12, $CHCl_3$). Anal. calcd for $C_{11}H_{11}O_2F_3$: C, 56.89; H, 4.77. Found: C, 56.85; H, 4.81%.

anti-**2a**: Pale yellow liquid. GC t_R 1.6 min. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=1.54$ (m, 3H, Me), 4.45–4.53 (m, 2H, H-4, H-5), 6.33 (s, 1H, H-2), 7.41–7.51 (m, 5H, aromatic H). Associations between Me-4 and H-2 in the NOESY spectrum. ^{13}C NMR (100 MHz): $\delta=14.18$ (Me), 72.87 (C-4), 76.28 (q, $^2J_{CF}=32$ Hz, C-5), 104.28 (C-2), 124.27 (q, $^1J_{CF}=281$ Hz, CF_3), 126.38, 128.86, 129.61 and 138.56 (aromatic C); $[\alpha]_D$ +20.5 (*c* 1.04, $CHCl_3$). Anal. calcd for $C_{11}H_{11}O_2F_3$: C, 56.89; H, 4.77. Found: C, 56.93; H, 4.84%.

5.2.2. (2*S*,4*S*,5*S*)-4-Methyl-2-*p*-tolyl-5-trifluoromethyl-1,3-dioxolane, *syn*-2b and (2*R*,4*S*,5*S*)-4-methyl-2-*p*-tolyl-5-trifluoromethyl-1,3-dioxolane, *anti*-2b. Obtained from **1** and *p*-tolualdehyde in 48 and 7% yield, respectively. Eluent for FC: EtOAc/petroleum ether, 1/18.

syn-**2b**: Pale yellow liquid. GC t_R 2.60 min. ^{1}H NMR (400 MHz): $\delta=1.59$ (dq, 3H, $J_{HH}=6.7$ Hz, $J_{HF}=1.8$ Hz, Me), 2.39 (s, 3H, Me), 4.37 (dq, 1H, $J_{HH}=J_{HF}=6.7$ Hz, H-5), 4.46 (dqq, 1H, $J_{HH}=6.7$ Hz, $J_{HF}=1.8$ Hz, H-4), 5.84 (s, 1H, H-2), 7.23 (d, 2H, $J=8.1$ Hz) and 7.43 (d, 2H, $J=8.1$ Hz) (aromatic H). ^{13}C NMR (75 MHz): $\delta=13.46$ (Me), 21.20 (Me), 74.62 (C-4), 75.27 (q, $^2J_{CF}=32$ Hz, C-5), 104.49 (C-2), 123.70 (q, $^1J_{CF}=282$ Hz, CF_3), 126.97, 129.10, 132.73 and 139.88 (aromatic C); $[\alpha]_D$ +14.8 (*c* 0.89, $CHCl_3$). Anal. calcd for $C_{12}H_{13}O_2F_3$: C, 58.53; H, 5.32. Found: C, 58.61; H, 5.14%.

anti-**2b**: Pale yellow liquid. GC t_R 2.20 min. ^{1}H NMR (400 MHz): $\delta=1.51$ (brd, 3H, $J=6.3$ Hz, Me), 2.39 (s, 3H, Me), 4.42–4.52 (m, 2H, H-4 and H-5), 6.29 (s, 1H, H-2), 7.22 (d, 2H, $J=7.9$ Hz) and 7.37 (d, 2H, $J=7.9$ Hz) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.23$ (Me), 21.62 (Me), 72.77 (C-4), 76.23 (q, $^2J_{CF}=31$ Hz, C-5), 104.35 (C-2), 124.25 (q, $^1J_{CF}=281$ Hz, CF_3), 126.26, 129.53, 135.58 and 139.52 (aromatic C); $[\alpha]_D$ +21.2 (*c* 0.44, $CHCl_3$). Anal. calcd for $C_{12}H_{13}O_2F_3$: C, 58.53; H, 5.32. Found: C, 58.66; H, 5.16%.

5.2.3. (2*S*,4*S*,5*S*)-4-Methyl-2-(2′-naphtyl)-5-trifluoromethyl-1,3-dioxolane, *syn*-2c and (2*R*,4*S*,5*S*)-4-methyl-2-(2′-naphtyl)-5-trifluoromethyl-1,3-dioxolane, *anti*-2c. Obtained from **1** and 2-naphtylaldehyde in 53 and 39% yield, respectively; eluent for FC: EtOAc/petroleum ether, 1/12.

syn-**2c**: White solid. GC t_R 15.5 min. ^{1}H NMR (400 MHz): $\delta=1.64$ (dq, 3H, $J_{HH}=6.6$ Hz, $J_{HF}=1.8$ Hz, Me), 4.44 (dq, 1H, $J_{HH}=J_{HF}=6.7$ Hz, H-5), 4.55 (dqq, 1H, $J_{HH}=6.6$ Hz, $J_{HF}=1.8$ Hz, H-4), 6.04 (s, 1H, H-2), 7.53 (m, 2H), 7.66 (dd, 1H, $J=8.5$ and 1.6 Hz), 7.87–7.92 (m, 3H) and 7.99 (s, 1H) (aromatic H). ^{13}C NMR (75 MHz): $\delta=13.54$ (Me), 74.80 (C-4), 75.74 (q, $^2J_{CF}=30$ Hz, C-5), 104.63 (C-2), 123.75 (q, $^1J_{CF}=280$ Hz, CF_3), 123.85, 126.33, 126.83, 127.30, 127.83, 128.42, 128.63, 132.92 and 134.30 (aromatic C); $[\alpha]_D$ +15.3 (*c* 0.77, $CHCl_3$). Anal. calcd for $C_{15}H_{13}O_2F_3$: C, 63.83; H, 4.64 Found: C, 63.66; H, 4.81%.

anti-**2c**: Colorless liquid which solidifies on standing. GC t_R 12.2 min. ^{1}H NMR (400 MHz): $\delta=1.55$–1.59 (m, 3H, Me), 4.49–4.57 (m, 2H, H-4 and H-5), 6.50 (s, 1H, H-2), 7.53–7.56 (m, 2H), 7.58 (dd, 1H, $J=8.5$ and 1.6 Hz), 7.85–7.93 (m, 3H) and 7.97 (brs, 1H) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.23$ (Me), 72.94 (C-4), 76.35 (q, $^2J_{CF}=31$ Hz, C-5), 104.44 (C-2), 124.31 (q, $^1J_{CF}=282$ Hz, CF_3), 123.76, 125.74, 126.84, 127.02, 128.18, 128.71, 128.92, 133.30, 134.14 and 135.87 (aromatic C); $[\alpha]_D$ +23.0 (*c* 1.07, $CHCl_3$). Anal. calcd for $C_{15}H_{13}O_2F_3$: C, 63.83; H, 4.64 Found: C, 63.72; H, 4.78%.

5.2.4. (2*S*,4*S*,5*S*)-2-(4-Bromophenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *syn*-2d and (2*R*,4*S*,5*S*)-2-(4-bromophenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *anti*-2d. Obtained from **1** and 4-bromo-benzaldehyde in 48 and 22% yield, respectively; eluent for FC: Et_2O/hexane, 15/85.

syn-**2d**: White solid. GC t_R 4.6 min. ^{1}H NMR (400 MHz): $\delta=1.59$ (dq, 3H, $J_{HH}=6.6$ Hz, $J_{HF}=1.8$ Hz, Me), 4.37 (dq, 1H, $J_{HH}=J_{HF}=6.6$ Hz, H-5), 4.47 (dqq, 1H, $J_{HH}=6.6$ Hz, $J_{HF}=1.8$ Hz, H-4), 5.82 (s, 1H, H-2), 7.41 (d, 2H, $J=8.4$ Hz) and 7.56 (d, 2H, $J=8.4$ Hz) (aromatic H). ^{13}C NMR (75 MHz): $\delta=13.44$ (Me), 74.80 (C-4), 75.23 (q, $^2J_{CF}=30$ Hz, C-5), 103.66 (C-2), 123.52 (q, $^1J_{CF}=280$ Hz, CF_3), 124.13, 128.70, 131.65 and 134.60 (aromatic C); $[\alpha]_D$ +16.7 (*c* 1.16, $CHCl_3$). Anal. calcd for $C_{11}H_{10}O_2BrF_3$: C, 42.47; H, 3.23. Found: C, 42.59; H, 3.18%.

anti-**2d**: Pale yellow liquid. GC t_R 3.5 min. ^{1}H NMR (400 MHz): $\delta=1.51$ (m, 3H, Me), 4.41–4.48 (m, 2H, H-4 and H-5), 6.26 (s, 1H, H-2), 7.35 (d, 2H, $J=8.4$ Hz) and 7.54 (d, 2H, $J=8.4$ Hz) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.14$ (Me), 72.96 (C-4), 76.26 (q, $^2J_{CF}=31$ Hz, C-5), 103.59 (C-2), 124.11 (q, $^1J_{CF}=281$ Hz, CF_3), 123.73, 127.98, 132.04, and 137.59 (aromatic C); $[\alpha]_D$ +21.1 (*c* 0.81, $CHCl_3$). Anal. calcd for $C_{11}H_{10}O_2BrF_3$: C, 42.47; H, 3.23. Found: C, 42.55; H, 3.15%.

5.2.5. (2*S*,4*S*,5*S*)-2-(3-Nitrophenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *syn*-2e and (2*R*,4*S*,5*S*)-2-(3-nitrophenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *anti*-2e. Obtained from **1** and 3-nitro-benzaldehyde in 40 and 22% yield, respectively; eluent for FC: EtOAc/hexane, 1/5.

syn-**2e**: Yellow liquid. TLC (eluent as above) R_f 0.29. ^{1}H NMR (400 MHz): $\delta=1.62$ (dq, 3H, $J_{HH}=6.6$ Hz, $J_{HF}=1.8$ Hz, Me), 4.43 (dq, 1H, $J_{HH}=J_{HF}=6.6$ Hz, H-5), 4.54 (dqq, 1H, $J_{HH}=6.6$ Hz, $J_{HF}=1.8$ Hz, H-4), 5.96 (s, 1H, H-2), 7.62 (t, 1H, $J=7.9$ Hz), 7.89 (dt, 1H, $J=7.9$ and 2.0 Hz), 8.30 (dt, 1H, $J=7.9$ and 2.0 Hz)

and 8.39 (t, 1H, $J=2.0$ Hz) (aromatic H). ^{13}C NMR (75 MHz): $\delta=13.32$ (Me), 75.09 (C-4), 75.30 (q, $^{2}J_{CF}=31$ Hz, C-5), 102.69 (C-2), 123.42 (q, $^{1}J_{CF}=281$ Hz, CF_3), 122.17, 124.60, 129.61, 132.92, 137.88 and 148.24 (aromatic C); $[\alpha]_D$ +16.4 (*c* 1.08, $CHCl_3$). Anal. calcd for $C_{11}H_{10}NO_4F_3$: C, 47.66; H, 3.63; N, 5.05. Found: C, 47.52; H, 3.71; N, 5.12%.

anti-**2e**: Pale yellow liquid TLC (eluent as above) R_f 0.43. ^{1}H NMR (400 MHz): $\delta=1.55$ (dq, 3H, $J_{HH}=8.2$ Hz, $J_{HF}=1.9$ Hz, Me), 4.47–4.49 (m, 2H, H-4 and H-5), 6.30 (s, 1H, H-2), 7.56 (t, 1H, $J=8.0$ Hz), 7.77 (brd, 1H, $J=8.0$ Hz), 8.20 (brd, 1H, $J=8.0$ Hz), 8.30 (t, 1H, $J=2.0$ Hz), (aromatic H). ^{13}C NMR (100 MHz): $\delta=13.64$ (Me), 72.89 (C-4), 75.99 (q, $^{2}J_{CF}=31$ Hz, C-5), 102.36 (C-2), 123.25 (q, $^{1}J_{CF}=280$ Hz, CF_3), 121.02, 124.04, 129.59, 132.10, 140.42, and 148.35 (aromatic C); $[\alpha]_D$ +24.3 (*c* 0.97, $CHCl_3$). Anal. calcd for $C_{11}H_{10}NO_4F_3$: C, 47.66; H, 3.63; N, 5.05. Found: C, 47.56; H, 3.68; N, 5.18%.

5.2.6. (2*S*,4*S*,5*S*)-2-(4-Nitrophenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *syn*-2f and (2*R*,4*S*,5*S*)-2-(4-nitrophenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *anti*-2f. Obtained from **1** and 4-nitro-benzaldehyde in 43 and 23% yield, respectively; eluent for FC: EtOAc/hexane, 1/3.

syn-**2f**: White solid. TLC (eluent as above) R_f 0.30. ^{1}H NMR (400 MHz): $\delta=1.61$ (dq, 3H, $J_{HH}=6.9$ Hz, $J_{HF}=1.8$ Hz, Me), 4.42 (dq, 1H, $J_{HH}=J_{HF}=6.9$ Hz, H-5), 4.54 (dqq, 1H, $J_{HH}=6.9$ Hz, $J_{HF}=1.8$ Hz, H-4), 5.96 (s, 1H, H-2), 7.71 (d, 2H, $J=8.8$ Hz) and 8.28 (d, 2H, $J=8.8$ Hz) (aromatic H). ^{13}C NMR (75 MHz): $\delta=13.37$ (Me), 75.14 (C-4), 75.34 (q, $^{2}J_{CF}=30$ Hz, C-5), 102.69 (C-2), 123.36 (q, $^{1}J_{CF}=280$ Hz, CF_3), 123.60, 127.89, 142.33 and 148.81 (aromatic C); $[\alpha]_D$ +16.9 (*c* 0.26, $CHCl_3$). Anal. calcd for $C_{11}H_{10}NO_4F_3$: C, 47.66; H, 3.63; N, 5.05. Found: C, 47.58; H, 3.65; N, 5.20%.

anti-**2f**: Colorless liquid. TLC (eluent as above) R_f 0.55. ^{1}H NMR (400 MHz): $\delta=1.55$ (m, 3H, Me), 4.42 (dqq, 1H, $J_{HH}=6.3$ Hz, $J_{HF}=1.5$ Hz, H-4), 4.48 (dq, 1H, $J_{HH}=J_{HF}=6.3$ Hz, H-5), 6.35 (s, 1H, H-2), 7.67 (d, 2H, $J=8.6$ Hz) and 8.27 (d, 2H, $J=8.6$ Hz) (aromatic H). ^{13}C NMR (75 MHz): $\delta=13.68$ (Me), 72.89 (C-4), 75.97 (q, $^{2}J_{CF}=31$ Hz, C-5), 102.47 (C-2), 123.52 (q, $^{1}J_{CF}=281$ Hz, CF_3), 123.72, 126.92, 144.89 and 148.47 (aromatic C); $[\alpha]_D$ +20.6 (*c* 0.43, $CHCl_3$). Anal. calcd for $C_{11}H_{10}NO_4F_3$: C, 47.66; H, 3.63; N, 5.05. Found: C, 47.70; H, 3.74; N, 5.09%.

5.2.7. (2*S*,4*S*,5*S*)-2-(3-Methoxyphenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *syn*-2g and (2*R*,4*S*,5*S*)-2-(3-methoxyphenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *anti*-2g. Obtained from **1** and 3-methoxy-benzaldehyde in 61 and 26% yield, respectively; eluent for FC: EtOAc/hexane, 1/8.

syn-**2g**: Colorless liquid which solidifies on standing. GC t_R 4.3 min. ^{1}H NMR (400 MHz): $\delta=1.60$ (dq, 3H, $J_{HH}=6.6$ Hz, $J_{HF}=1.8$ Hz, Me), 3.84 (s, 3H, OMe), 4.37 (dq, 1H, $J_{HH}=J_{HF}=6.6$ Hz, H-5), 4.48 (dqq, 1H, $J_{HH}=6.6$ Hz, $J_{HF}=1.8$ Hz, H-4), 5.85 (s, 1H, H-2), 6.97 (dd, 1H, $J=8.0$ and 1.6 Hz), 7.11 (d, 1H, $J=1.6$ Hz), 7.12 (d, 1H, $J=8.0$ Hz) and 7.33 (t, 1H, $J=8.0$) (aromatic H). ^{13}C NMR (75 MHz): $\delta=13.47$ (Me), 55.23 (OMe), 74.72 (C-4), 75.70 (q, $^{2}J_{CF}=31$ Hz, C-5), 104.26 (C-2), 123.58 (q, $^{1}J_{CF}=283$ Hz, CF_3), 111.94, 115.99, 119.45, 129.56, 136.90 and 159.72 (aromatic C); $[\alpha]_D$ +13.7 (*c* 1.12, $CHCl_3$). Anal. calcd for $C_{12}H_{13}O_3F_3$: C, 54.96; H, 4.99. Found: C, 55.08; H, 4.77%.

anti-**2g** Pale yellow liquid. GC t_R 3.7 min. ^{1}H NMR (400 MHz): $\delta=1.52$ (dm, 3H, $J=6.6$ Hz, Me), 3.84 (s, 3H, Me), 4.46 (dq, 1H, $J_{HH}=J_{HF}=6.6$ Hz, H-5), 4.47 (m, 1H, H-4), 6.29 (s, 1H, H-2), 6.92 (dd, 1H, $J=7.8$ and 2.3 Hz), 7.01 (d, 1H, $J=2.3$ Hz), 7.06 (d, 1H, $J=7.8$ Hz) and 7.32 (t, 1H, $J=7.8$ Hz) (aromatic H). ^{13}C NMR (75 MHz): $\delta=13.70$ (Me), 55.22 (OMe), 72.38 (C-4), 75.76 (q, $^{2}J_{CF}=30$ Hz, C-5), 103.63 (C-2), 123.81 (q, $^{1}J_{CF}=281$ Hz, CF_3), 111.20, 114.79, 118.07, 129.62, 135.73 and 159.75 (aromatic C); $[\alpha]_D$ +22.6 (*c* 0.84, $CHCl_3$). Anal. calcd for $C_{12}H_{13}O_3F_3$: C, 54.96; H, 4.99. Found: C, 55.14; H, 4.81%.

5.2.8. (2*S*,4*S*,5*S*)-2-(4-Methoxyphenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *syn*-2h and (2*R*,4*S*,5*S*)-2-(4-methoxyphenyl)-4-methyl-5-trifluoromethyl-1,3-dioxolane, *anti*-2h. Obtained from **1** and 4-methoxy-benzaldehyde in 66 and 15% yield, respectively; eluent for FC: Et_2O/hexane, 2/8.

syn-**2h**: Pale yellow solid. GC t_R 5.2 min. ^{1}H NMR (400 MHz): $\delta=1.59$ (dq, 3H, $J_{HH}=6.9$ Hz, $J_{HF}=1.8$ Hz, Me), 3.83 (s, 3H, OMe), 4.36 (dq, 1H, $J_{HH}=J_{HF}=6.9$ Hz, H-5), 4.45 (dqq, 1H, $J_{HH}=6.9$ Hz, $J_{HF}=1.8$ Hz, H-4), 5.83 (s, 1H, H-2), 6.94 (d, 2H, $J=8.7$ Hz) and 7.47 (d, 2H, $J=8.7$ Hz) (aromatic H). ^{13}C NMR (100 MHz): $\delta=13.87$ (Me), 55.65 (OMe), 74.94 (C-4), 75.53 (q, $^{2}J_{CF}=30$ Hz, C-5), 104.79 (C-2), 124.16 (q, $^{1}J_{CF}=280$ Hz, CF_3), 114.30, 128.11, 128.99 and 161.40 (aromatic C); $[\alpha]_D$ +15.7 (*c* 0.48, $CHCl_3$). Anal. calcd for $C_{12}H_{13}O_3F_3$: C, 54.96; H, 4.99. Found: C, 55.15; H, 4.84%.

anti-**2h**: Pale yellow liquid. GC t_R 4.1 min. ^{1}H NMR (400 MHz): $\delta=1.51$ (m, 3H, Me), 3.82 (s, 3H, OMe), 4.42–4.54 (m, 2H, H-4 and H-5), 6.26 (s, 1H, H-2), 6.93 (d, 2H, $J=8.5$ Hz) and 7.39 (d, 2H, $J=8.5$ Hz) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.30$ (Me), 55.71 (OMe), 72.80 (C-4), 76.25 (q, $^{2}J_{CF}=31$ Hz, C-5), 104.26 (C-2), 124.26 (q, $^{1}J_{CF}=281$ Hz, CF_3), 114.23, 127.77, 130.58 and 160.77 (aromatic C); $[\alpha]_D$ +19.6 (*c* 0.56, $CHCl_3$). Anal. calcd for $C_{12}H_{13}O_3F_3$: C, 54.96; H, 4.99. Found: C, 55.04; H, 4.81%.

5.3. Reductive ring-opening reactions of acetals with $TiCl_4$/Et_3SiH(D). General procedure

1 M $TiCl_4$ solution in CH_2Cl_2 (0.26 mL) was added dropwise over ca. 2.5 min to a solution of the 1,3-dioxolane (0.5 mmol) and Et_3SiH(D) (0.55 mmol) in dry CH_2Cl_2 (2.5 mL) at −78°C under N_2 and the mixture was stirred for 15 min. After quenching with MeOH (0.2 mL) and further stirring for 5 min, the reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with 1 M HCl and with saturated NaCl, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave the reaction product which was purified by flash chromatography.

5.3.1. (2*S*,3*S*)-3-[(*R*)-α-^{2}H]-Benzyl-1,1,1-trifluorobutan-2-ol 3a. See Table 1 for yields from *syn*-**2a** and *anti*-**2a**.

Pale yellow liquid. GC t_R 3.9 min. Eluent for FC: EtOAc/petroleum ether, 1/7. ^{1}H NMR (400 MHz): $\delta=1.34$ (d, 3H, $J=6.2$ Hz, Me), 2.65 (brs, 1H, OH), 3.82–3.88 (m, 1H) and 4.10–4.15 (m, 1H) (H-2 and H-3), 4.51 (brs, 0.94H, CH_S-Ar), 4.64 (brs, 0.06H, CH_R-Ar), 7.31–7.40 (m, 5H, aromatic H). ^{13}C NMR (100 MHz): $\delta=14.51$ (Me), 71.28 (t, $^1J_{CD}=21$ Hz, CHD), 72.33 (q, $^2J_{CF}=29$ Hz, C-2), 73.70 (C-3), 124.79 (q, $^1J_{CF}=281$ Hz, CF_3), 128.29, 128.45, 128.96 and 137.82 (aromatic C); $[\alpha]_D$ +20.6 (*c* 0.43, $CHCl_3$).

5.3.2. (2*S*,3*S*)-3-[(*R*)-α-^{2}H]-(4-Methylbenzyloxy)-1,1,1-trifluorobutan-2-ol, 3b. See Table 1 for yields from *syn*-**2b** and *anti*-**2b**.

Pale yellow liquid. GC t_R 5.3 min. Eluent for FC: EtOAc/petroleum ether, 1/6. ^{1}H NMR (300 MHz): $\delta=1.29$ (d, 3H, $J=6.3$ Hz, Me), 2.34 (s, 3H, Me), 2.58 (brs, 1H, OH), 3.76–3.84 (m, 1H) and 4.02–4.08 (m, 1H) (H-2 and H-3), 4.43 (brs, 0.93H, CH_S-Ar), 4.56 (brs, 0.07H, CH_R-Ar), 7.15 (d, 2H, $J=8.1$ Hz) and 7.21 (d, 2H, $J=8.1$ Hz) (aromatic H). ^{13}C NMR (75 MHz): $\delta=14.04$ (Me), 21.08 (Me), 70.75 (t, $^1J_{CD}=21$ Hz, CHD), 71.88 (q, $^2J_{CF}=31$ Hz, C-2), 73.06 (C-3), 124.39 (q, $^1J_{CF}=281$ Hz, CF_3), 128.05, 129.22, 134.36 and 137.83 (aromatic C); $[\alpha]_D$ +8.2 (*c* 1.12, $CHCl_3$).

5.3.3. (2*S*,3*S*)-3-[(*R*)-α-^{2}H]-3-(Naphtalen-2-ylmethoxy)-1,1,1-trifluorobutan-2-ol, 3c. See Table 1 for yields from *syn*-**2c** and *anti*-**2c**.

White solid. TLC: Eluent as above, R_f 0.32. ^{1}H NMR (400 MHz): $\delta=1.37$ (d, 3H, $J=6.4$ Hz, Me), 2.62 (brd, 1H, $J=5.3$ Hz, OH), 3.91 (qd, 1H, $J=6.3$ and 4.2 Hz, H-3), 4.12–4.19 (m, 1H, H-2), 4.68 (brs, 0.96H, CH_S-Ar), 4.80 (brs, 0.04H, CH_R-Ar), 7.47–7.52 (m, 3H), 7.79 (s, 1H), 7.77–7.88 (m, 3H) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.65$ (Me), 71.33 (t, $^1J_{CD}=21$ Hz, CHD), 72.49 (q, $^2J_{CF}=29$ Hz, C-2), 73.45 (C-3), 124.72 (q, $^1J_{CF}=280$ Hz, CF_3), 126.01, 126.49, 126.66, 127.03, 128.13, 128.28, 128.80, 133.50, 133.64 and 135.30 (aromatic C); $[\alpha]_D$ +8.4 (*c* 0.45, $CHCl_3$).

5.3.4. (2*S*,3*S*)-3-[(*R*)-α-^{2}H]-(4-Bromobenzyloxy)-1,1,1-trifluorobutan-2-ol, 3d. See Table 1 for yields from *syn*-**2d** and *anti*-**2d**.

Pale yellow liquid. Eluent for FC: EtOAc/hexane, 1/6. ^{1}H NMR (400 MHz): $\delta=1.34$ (d, 3H, $J=6.3$ Hz, Me), 2.62 (brd, 1H, $J=5.1$ Hz, OH), 3.83 (qd, 1H, $J=6.3$ and 4.3 Hz, H-3), 4.06–4.15 (m, 1H, H-2), 4.46 (brs, 0.95H, CH_S-Ar), 4.58 (brs, 0.05H, CH_R-Ar), 7.23 (d, 2H, $J=8.3$ Hz) and 7.50 (d, 2H, $J=8.3$ Hz) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.63$ (Me), 70.46 (t, $^1J_{CD}=22$ Hz, CHD), 72.43 (q, $^2J_{CF}=29$ Hz, C-2), 73.88 (C-3), 124.75 (q, $^1J_{CF}=280$ Hz, CF_3), 122.28, 129.81, 132.04 and 136.90 (aromatic C); $[\alpha]_D$ +8.4 (*c* 1.01, $CHCl_3$).

5.3.5. (2*S*,3*S*)-3-[(*R*)-α-^{2}H]-(3-Nitrobenzyloxy)-1,1,1-trifluorobutan-2-ol, 3e. See Table 1 for yields from *syn*-**2e** and *anti*-**2e**.

Pale yellow liquid. Eluent for FC: EtOAc/petroleum ether, 1/2. ^{1}H NMR (400 MHz): $\delta=1.36$ (d, 3H, $J=6.3$ Hz, Me), 2.47 (brd, 1H, $J=4.8$ Hz, OH), 3.86 (qd, 1H, $J=6.3$ and 4.6 Hz, H-3), 4.06–4.14 (m, 1H, H-2), 4.58 (brs, 0.91H, CH_S-Ar), 4.70 (brs, 0.09H, CH_R-Ar), 7.52 (t, 1H, $J=7.8$ Hz), 7.66 (d, 1H, $J=7.8$ Hz), 8.15 (d, 1H, $J=7.8$ Hz), and 8.21 (s, 1H) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.44$ (Me), 69.49 (t, $^1J_{CD}=22$ Hz, CHD), 72.20 (q, $^2J_{CF}=30$ Hz, C-2), 74.07 (C-3), 124.33 (q, $^1J_{CF}=283$ Hz, CF_3), 122.17, 122.70, 129.41, 133.37, 139.91 and 148.32 (aromatic C); $[\alpha]_D$ +8.3 (*c* 0.82, $CHCl_3$).

5.3.6. (2*S*,3*S*)-3-[(*R*)-α-^{2}H]-(4-Nitrobenzyloxy)-1,1,1-trifluorobutan-2-ol, 3f. See Table 1 for yields from *syn*-**2f** and *anti*-**2f**.

Pale yellow liquid. Eluent for FC: EtOAc/hexane, 1/3. ^{1}H NMR (400 MHz): $\delta=1.39$ (d, 3H, $J=6.4$ Hz, Me), 2.59 (brd, 1H, $J=5.1$ Hz, OH), 3.89 (qd, 1H, $J=6.4$ and 4.6 Hz, H-3), 4.13 (qdd, 1H, $J=6.9$, 5.1, and 4.6 Hz, H-2), 4.62 (brs, 0.90H, CH_S-Ar), 4.74 (brs, 0.10H, CH_R-Ar), 7.52 (d, 2H, $J=8.5$ Hz) and 8.23 (d, 2H, $J=8.5$ Hz) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.49$ (Me), 69.49 (t, $^1J_{CD}=22$ Hz, CHD), 72.14 (q, $^2J_{CF}=27$ Hz, C-2), 74.22 (C-3), 124.40 (q, $^1J_{CF}=281$ Hz, CF_3), 123.60, 127.77, 145.34 and 147.36 (aromatic C); $[\alpha]_D$ +10.4 (*c* 0.72, $CHCl_3$).

5.3.7. (2*S*,3*S*)-3-[(*R*)-α-^{2}H]-(3-Methoxybenzyloxy)-1,1,1-trifluorobutan-2-ol, 3g. See Table 1 for yields from *syn*-**2g** and *anti*-**2g**.

Pale yellow liquid. GC t_R 11.0 min (eluent for FC: EtOAc/petroleum ether, 1/5). ^{1}H NMR (400 MHz): $\delta=1.34$ (d, 3H, $J=6.4$ Hz, Me), 2.59 (brd, 1H, $J=5.0$ Hz, OH), 3.81–3.88 (m, 1H, H-3), 3.84 (s, 3H, OMe), 4.11–4.15 (m, 1H, H-2), 4.49 (brs, 0.91H, CH_S-Ar), 4.62 (brs, 0.09H, CH_R-Ar), 6.87 (dd, 1H, $J=8.1$ and 2.5 Hz), 6.91 (s, 1H), 6.92 (d, 1H, $J=8.1$ Hz) and 7.29 (t, 1H, $J=8.1$ Hz) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.15$ (Me), 55.19 (OMe), 70.65 (t, $^1J_{CD}=21$ Hz, CHD), 71.88 (q, $^2J_{CF}=30$ Hz, C-2), 73.24 (C-3), 124.37 (q, $^1J_{CF}=276$ Hz, CF_3), 113.27, 113.52, 120.03, 129.62, 139.02 and 159.78 (aromatic C); $[\alpha]_D$ +9.8 (*c* 0.87, $CHCl_3$).

5.3.8. (2*S*,3*S*)-3-[(*R*)-α-^{2}H]-(4-Methoxybenzyloxy)-1,1,1-trifluorobutan-2-ol, 3h. See Table 1 for yields from *syn*-**2h** and *anti*-**2h**.

Pale yellow liquid. GC t_R 11.0 min. Eluent for FC: EtOAc/petroleum ether, 1/5.

^{1}H NMR (400 MHz): $\delta=1.31$ (dd, 3H, $J=6.4$ and 0.9 Hz, Me), 2.65 (brd, 1H, $J=5.1$ Hz, OH), 3.79–3.83 (m, 4H, H-3 and OMe), 4.06–4.10 (m, 1H, H-2), 4.43 (brs, 0.91H, CH_S-Ar), 4.56 (brs, 0.09H, CH_R-Ar), 6.91 (d, 2H, $J=8.6$ Hz) and 7.28 (d, 2H, $J=8.6$ Hz) (aromatic H). ^{13}C NMR (100 MHz): $\delta=14.14$ (Me), 55.26 (OMe), 70.47 (t,

$^1J_{CD}$ = 21 Hz, CHD), 71.84 (q, $^2J_{CF}$ = 28 Hz, C-2), 72.81 (C-3), 124.38 (q, $^1J_{CF}$ = 279 Hz, CF_3), 113.92, 128.20, 129.12 and 159.43 (aromatic C); $[\alpha]_D$ +8.8 (*c* 0.89, $CHCl_3$).

5.4. 3-Benzyloxy-4,4,4-trifluorobutan-2-ol, 4

To a solution of **1** (302 mg, 2.1 mmol) in dry THF (10 ml) potassium *tert*-butoxide (236 mg, 2.1 mmol) was added and the mixture was heated at reflux for 15 min with stirring. Benzyl bromide (0.25 ml, 2.1 mmol) was then added and the mixture was refluxed for 2.5 h, cooled to room temperature, diluted with ethyl acetate (15 ml), washed with 1N HCl (2×20 ml) and saturated NaCl (1×15ml). The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. Flash column chromatography (silica gel, EtOAc/hexane, 1/5) gave pure **4** as a pale yellow liquid (330 mg, 67% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (d, *J* = 6.2 Hz, 3H, Me), 2.00 (brs, 1H, OH), 3.80 (m, 1H) and 4.05 (m, 1H) (H-2 and H-3), 4.64 and 4.90 (AB syst., *J* = 11.3 Hz, 2H, CH_2Ph), 7.31–7.41 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.97 (Me), 66.32 (C-2), 75.20 (CH_2); 80.17 (q, $^2J_{CF}$ = 26 Hz, C-3), 124.73 (q, $^1J_{CF}$ = 283 Hz, CF_3), 128.14, 128.34, 128.59 and 136.79 (aromatic C); $[\alpha]_D$ −21.1 (*c* 1.14, $CHCl_3$). Anal. calcd for $C_{11}H_{13}O_2F_3$: C, 56.41; H, 5.59. Found: C, 56.16; H, 5.34%.

5.5. (*R*)-(α-^{2}H)Benzyl alcohol, 5

To a solution of oxalyl chloride (0.049 ml, 0.62 mmol) in dry CH_2Cl_2 (1 ml) at −78°C under N_2, dimethyl sulfoxide (0.08 ml, 1.25 mmol) was added, keeping the temperature below −50°C. The mixture was stirred for 5 min and a solution of compound **3a** (H_R = D) (135 mg, 0.57 mmol) in CH_2Cl_2 (0.5 ml) was added over 10 min. The mixture was stirred for 15 min, then treated with Et_3N (0.4 ml) and the stirring was continued for additional 15 min. The acetone-solid carbon dioxide bath was removed and the reaction was quenched with water (2 ml). The aqueous layer was extracted with CH_2Cl_2 (3×5 ml) and the combined organic layers were dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave crude 3-[(*R*-α-^{2}H)benzyloxy]-1,1,1-trifluorobutan-2-one (180 mg) which was used in the next step without further purification.

The crude 3-[(*R*-α-^{2}H)benzyloxy]-1,1,1-trifluorobutan-2-one prepared as above (180 mg) was dissolved in THF (0.5 ml) and carefully added to a suspension of NaH (296 mg, 50% dispersion in mineral oil) in THF (5 ml) with stirring under N_2. The mixture was stirred at rt for 15 min and then refluxed for 3 h. After cooling to rt the reaction mixture was treated with MeOH (0.75 ml) and extracted with water (3×3 ml). The combined aqueous solutions were acidified with 10% HCl (pH ca. 1), saturated with solid NaCl and extracted with ethyl acetate (3×5 ml). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure to afford 2-[(*R*-α-^{2}H)benzyloxy]propanoic acid as a yellow liquid (70 mg, 66% yield after two steps)

2-[(*R*-α-^{2}H)benzyloxy]propanoic acid: ^{1}H NMR (400 MHz) δ: 1.52 (d, 3H, *J* = 6.9 Hz, Me); 4.14 (q, 1H, *J* = 6.9 Hz, H-2); 4.70 and 4.75 (br s, 0.5 H each, C*H*D); 5.65 (br, 1H, COO*H*); 7.33–7.39 (m, 5H, aromatic H).

A solution of 2-[(*R*-α-^{2}H)benzyloxy]propanoic acid prepared as above (70 mg, 0.38 mmol) in dry THF (1.2 ml) was placed in a three necked round-bottom flask equipped with a condenser, treated with Et_3N (0.050 ml) and stirred at rt under N_2 for 15 min. Then diphenylphosphoazidate (DPPA) (0.087 ml, 0.38 mmol) was added in one portion and the reaction mixture was stirred for additional 30 min. The temperature was quickly raised to 60°C using a pre-heated water bath and water (0.80 ml) was added. The reaction was stirred at 60°C for 30 min, cooled to rt, diluted with ethyl acetate (5 ml) and washed with 1 M HCl (2×4 ml), saturated NaCl (1×4 ml), saturated $NaHCO_3$ (2×4 ml) and saturated NaCl (1×4 ml). The separated organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography (eluent: EtOAc/hexane, 3/5) to give (*R*)-(α-^{2}H)benzyl alcohol (**5**) as a pale yellow liquid (10 mg, 24% yield).

5: ^{1}H NMR (400 MHz) δ: 2.08 (brs, 1H, OH); 4.78 (brt, 1H, $^1J_{HD}$ = 1.87 Hz, C*H*D); 7.37–7.39 (m, 5H, aromatic H); ^{13}C NMR (100 MHz) δ: 65.33 (t, $^1J_{CD}$ = 21 Hz, CHD); 127.42, 128.04, 128.95, 141.25 (aromatic C).

5.6. Cartesian coordinates (in Å) of the species reported in Fig. 1, optimized at the B3LYP/LANL2DZ level

5.6.1. *syn*-2a.

H	−0.386915	−0.140704	−2.415602
C	−0.386689	−0.140804	−1.315290
O	1.059449	−0.140914	−0.899935
C	1.436614	1.217954	−0.534505
C	0.191991	2.087154	−0.908886
O	−0.905997	1.111211	−0.806424
H	2.323340	1.518926	−1.103657
H	0.315204	2.367554	−1.967336
C	1.854571	1.228077	0.941731
C	−0.154544	3.314631	−0.074117
H	−0.345020	3.044397	0.967855
H	−1.059687	3.776088	−0.482264
H	0.656467	4.050706	−0.105154
F	0.815744	0.958889	1.840339
F	2.863022	0.300810	1.200860
F	2.379585	2.489363	1.296669
C	−1.120265	−1.324467	−0.753486
C	−2.474300	−3.572523	0.271834
C	−1.539835	−2.353281	−1.618093
C	−1.380559	−1.419997	0.629775
C	−2.056870	−2.540846	1.138195
C	−2.214944	−3.478049	−1.107919
H	−1.339036	−2.280730	−2.685698
H	−1.058518	−0.622672	1.291938
H	−2.257693	−2.614107	2.204164
H	−2.535643	−4.270747	−1.779171
H	−2.996301	−4.439743	0.669548

5.6.2. *anti*-2a.

C	−0.682201	0.399421	−0.695201
O	−0.684102	0.407434	0.791163
C	0.696018	0.389595	1.260094
C	1.541837	0.085493	−0.014728
O	0.693216	0.648705	−1.083716
H	0.806480	−0.393763	2.016818
H	1.565845	−1.008689	−0.124025
C	0.979840	1.721506	1.969161
C	2.944552	0.667422	−0.147019
H	2.925714	1.760112	−0.114796
H	3.366356	0.357791	−1.108893
H	3.597686	0.301163	0.652790
F	0.932081	2.839821	1.135366
F	0.072946	1.949639	3.006725
F	2.259020	1.705617	2.564212
H	−1.266461	1.262492	−1.027659
C	−1.225206	−0.921141	−1.220928
C	−2.304914	−3.306652	−2.271937
C	−0.837637	−1.370135	−2.501004
C	−2.157497	−1.665890	−0.470126
C	−2.693694	−2.856603	−0.995318
C	−1.374604	−2.561522	−3.022644
H	−0.115430	−0.793863	−3.073030
H	−2.447209	−1.317331	0.516605
H	−3.410418	−3.429415	−0.411564
H	−1.069670	−2.906093	−4.007942
H	−2.721192	−4.226178	−2.676706

5.6.3. *syn*-A.

H	−1.640038	0.685598	−1.575920
C	−1.633088	0.687866	−0.482531
O	−0.017088	0.689044	−0.215567
C	0.324585	2.032413	0.259212
C	−0.912377	2.887112	−0.133895
O	−2.008955	1.926943	0.079776
H	1.225121	2.372204	−0.255275
H	−0.822846	3.088000	−1.212617
C	0.661655	2.006773	1.760453
C	−1.211619	4.170812	0.628103
H	−1.405378	3.972577	1.685258
H	−2.100536	4.640867	0.195578
H	−0.374122	4.872434	0.548261
F	−0.437001	1.801394	2.603164
F	1.594736	1.023753	2.073879
F	1.228429	3.240308	2.130374
C	−2.338906	−0.466494	0.141328
C	−3.722507	−2.640984	1.271224
C	−2.782575	−1.525888	−0.678497
C	−2.599468	−0.491622	1.529331
C	−3.287293	−1.578269	2.089516
C	−3.472974	−2.611848	−0.113616
H	−2.589022	−1.507255	−1.747944
H	−2.270364	0.331218	2.154372
H	−3.483158	−1.601307	3.158211
H	−3.810788	−3.427507	−0.747060
H	−4.252366	−3.482851	1.710147
Ti	1.387286	−0.907795	−0.989652
Cl	2.762949	−2.493654	−1.771004
Cl	0.768449	−2.044262	0.816313
Cl	0.068029	−0.875513	−2.812053
Cl	2.964307	0.689387	−0.935896

5.6.4. *anti*-A.

C	0.676809	−0.073213	−1.626209
O	0.675772	−0.071741	−0.063715
C	2.089998	−0.073178	0.336949
C	2.747465	−0.957031	−0.746629
O	1.968994	−0.626476	−1.957448
H	2.159644	−0.514097	1.331308
H	2.530122	−1.999214	−0.472854
C	2.630663	1.367368	0.434691
C	4.233783	−0.793355	−1.048849
H	4.468662	0.221305	−1.379420
H	4.504624	−1.487119	−1.851306
H	4.838564	−1.031439	−0.166290
F	2.725336	2.019661	−0.802494
F	1.840303	2.177053	1.247404
F	3.915976	1.358297	0.996346
H	0.643236	0.984983	−1.900091
C	−0.451588	−0.866569	−2.216619
C	−2.555807	−2.322800	−3.394121
C	−1.576031	−0.192355	−2.734169
C	−0.372412	−2.272015	−2.312727
C	−1.422658	−2.997376	−2.894793
C	−2.628381	−0.919625	−3.318385
H	−1.634004	0.891838	−2.678846
H	0.510561	−2.789197	−1.948830
H	−1.362482	−4.080482	−2.962537
H	−3.495753	−0.395943	−3.711198
H	−3.369529	−2.886305	−3.843977
Ti	−1.194243	0.305764	1.374987
Cl	0.308367	−0.002942	3.007713
Cl	−1.398995	2.095832	0.036756
Cl	−1.986897	−1.634043	0.682926
Cl	−2.878007	0.867646	2.723047

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