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Convenient synthesis of optically active deuterated primary alcohols via deuteride reduction of acetals derived from homochiral (1*R**,2*R**)-3,3,3-trifluoro-1-phenylpropane-1,2-diols

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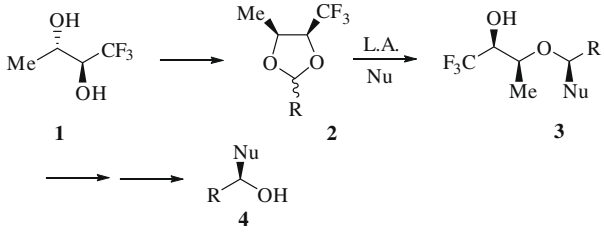
ABSTRACT

(1*R*)-1-Deuterated alcohols with high enantiomeric excess were prepared via $TiCl_4/Et_3SiD$ reduction of acetals arising from the reaction of aldehydes with (1*S*,2*S*)-3,3,3-trifluoro-1-phenylpropane-1,2-diol **9**. Such a chiral auxiliary was synthesized in an enantiomerically pure form starting from L-mandelic acid. Due to its benzylic nature, it was easily removed from the reaction product of the reductive 1,3-dioxolane ring-cleavage to afford the desired α-deuterated alcohol.

1. Introduction

Chiral deuterated primary alcohols are used extensively for investigating mechanisms in chemical and biological processes.[1] To obtain enantiomerically pure R–CHD–OH compounds, two chemical† approaches are usually adopted; either the stereoselective hydrogenation of the previously deuterated formyl group[2] or the deuteride reduction of the non-deuterated aldehyde precursor.[3] The latter route appears to be more advantageous since it does not require a synthetic step for preparing the –CD=O group. Nevertheless, it also entails some difficulties such as the synthesis of the deuterated chiral reducing agent[3d] and the availability of the chiral catalyst for the enantioselective deuteride transfer from a common donor (e.g., $NaBD_4$).[3a–c] It should be noted that some alternative isotopic labelling strategies to prepare chiral 1-deuterated alcohols have already been reported, for example, the use of Pd(II)-catalyzed rearrangement of allylic acetates[4a] and Zn/Li transmetallation on chiral α-carbamoyloxy organolithiums followed by treatment with D_2O.[4b]

In principle, the use of a chiral auxiliary capable of forming an aldehyde adduct, which then undergoes regio- and diastereoselective deuteride reduction, can be envisaged as an alternative to obtain optically active (1-^{2}H)alcohols. However, to the best of our knowledge, only one example[5] of such strategy has been reported so far.



Scheme 1. Stereoselective nucleophilic ring-opening of 2-substituted *cis*-4-methyl-5-trifluoromethyl dioxolanes **2**. [6a]

In previous papers,[6a–c] we have reported that 1,3-dioxolanes **2** (Scheme 1), derived by reaction of aldehydes with (2*S*,3*S*)-1,1,1-trifluorobutane-2,3-diol **1**, undergo Lewis acid-promoted nucleophilic ring-opening reactions with the same regio- and stereoselectivities independent of the configuration of the acetal carbon atom. In spite of the good yields and the high stereoselectivity observed in the ring-cleavage of **2**, the removal of the chiral auxiliary from **3** to obtain enantiomerically enriched alcohols **4** required a laborious three-step procedure which greatly limited the use of the reaction sequence shown in Scheme 1 for synthetic purposes.

Taking this into account, we thought that the use of a properly 1-substituted 3,3,3-trifluoropropane-1,2-diol could offer an easier way to liberate the alcohol from the product of the 1,3-dioxolane reduction. Herein, we report the synthesis of (1*S*,2*S*)-3,3,3-trifluoro-1-phenylpropane-1,2-diol **9** and its application for preparing α-deuterated primary alcohols with high enantiomeric excess.

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† Biochemical enzymatic methods suffer the limitation that the deuterated stereocentre is obtained in one enantiomeric form with the result that a chemical multistep process (configuration inversion) is necessary to provide the other enantiomer (e.g., Ref. 15).

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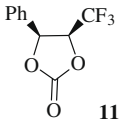
2. Results and discussion

Aldehyde **6**,[7] prepared from L-mandelic acid **5** (enantiomeric purity = 99%), was allowed to react with (trifluoromethyl)trimethylsilane in the presence of a catalytic amount of tetra(*n*-butyl)-ammonium fluoride (TBAF)[6d,8] to give a mixture of the fully protected 3,3,3-trifluoro-1-phenylpropane-1,2-diols **7** and **8** in ca. 55:45 ratio (Scheme 2). After chromatographic separation of the two diastereoisomers, their quantitative deprotection furnished the pure diols **9** and **10** in satisfactory overall yields (ca. 40% each of them from aldehyde **6**).



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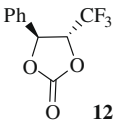

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The relative configurations of **9** (1*S*,2*S*) and **10** (1*S*,2*R*) were established on the basis of ^{1}H NMR data (^{1}H–^{1}H coupling constants and NOESY of their cyclic carbonates, that is, **11** and **12**, respectively).[6d,9] Taking into account that the stereocentre of the starting L-mandelic acid was not involved in the reactions leading to both diastereomeric diols, the absolute (1*S*,2*S*)-configuration was assigned to **9**. The enantiomeric purity of this compound was confirmed to be ⩾99% by inspection of the ^{1}H NMR spectrum of its MTPA diester in comparison with that of *rac*-**9** diester prepared from (D,L)-mandelic acid.

Compound **9** was reacted with octanal **13a** (Scheme 3) in refluxing toluene in the presence of catalytic amount of *p*-toluenesulfonic acid to provide a *syn*/*anti* mixture of the two diastereomeric 1,3-dioxolanes,[6] that is, **14a** (*syn*) and its epimer at C-2 (*anti*), in 90% global yield.

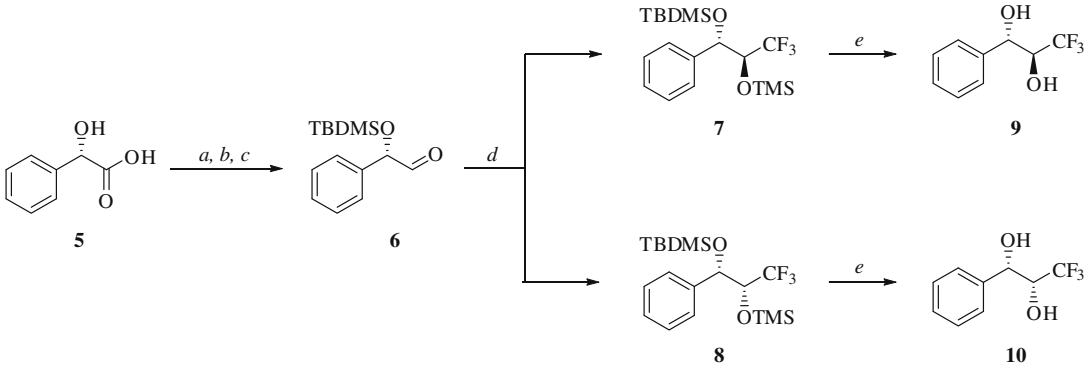
Both were isolated by flash chromatography (Table 1) after which **14a** was then subjected to reductive ring-opening reaction using stoichiometric amount of $TiCl_4$ and Et_3SiD[10] (*D* > 98%). Ether **15a** was obtained as the only reaction product in agreement with a high regioselectivity of the nucleophilic dioxolane cleavage. The ^{1}H NMR spectrum of **15a** exhibited two broad triplets at 3.29 and 3.37 ppm (corresponding to protons H_S and H_R of O–CHD–R, respectively)[6] with relative intensities 95:5, which were indicative of high diastereoselectivity in the invertive attack of the formal deuteride anion to the acetalic carbon. The reductive ring-opening of the *anti*-dioxolane under the above reaction conditions furnished the same product **15a** as in the case of the *syn*-isomer, the yield and diastereomeric excess being practically identical for both dioxolanes. Such behaviour of the C-2 epimeric 1,3-dioxolanes (mentioned above with regard to the nucleophilic cleavage of acetals derived from the diol **1**, Scheme 1) has been explained on the basis of kinetics and reactivity considerations.[6a] It suggests the use of the diastereomeric mixture of acetals to obtain the ring-opening product suited for the next synthetic steps. Finally, the removal of the chiral auxiliary from **15a** was accomplished by its conversion into acetate **16a** which in turn was treated with boron tribromide in dichloromethane at 0 °C.[11] The resultant α-monodeuterated 1-octanol **17a** was isolated in ca 70% overall yield. Its configuration at C1 was proven to be (*R*) by the MTPA ester method using racemic monodeuterated 1-octanol and an authentic sample of (*R*)-(1-^{2}H)octanol[6b] as reference compounds.

The procedure described here was validated by the experiments reported in Table 1 as a general method for preparing

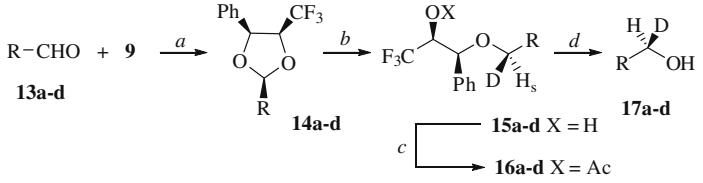
Table 1
Isolated yields of products from reactions of Scheme 3

Entry	**13** (R=)	**14**[a]	**15**	**17**[b] (% ee)
a	nC_7H_{15}	72 (80:20)	89 (95:5)	70[6b] (90)
b	$C_6H_5CH_2CH_2$	63 (76:24)	87 (94:6)	76[12] (88)
c	$C_6H_5CH_2$	35 (63:37)	85 (92:8)	74[13] (84)
d	Cyclohexyl	37 (60:40)	97 (96:4)	72[14] (92)

[a] The *syn*/*anti* ratios of the dioxolane mixture giving **14** are in parentheses.
[b] The (*R*)-configuration proved by ^{1}H NMR analysis of the corresponding MPTA esters.



Scheme 2. Reagents and conditions: (a) MeOH, TsOH, rt; (b) TBDMSCl, imidazole, DMF, rt; (c) DIBAL-H, Et_2O, −78 °C; (d) Me_3SiCF_3, cat. TBAF, THF, 0 °C; (e) TBAF, THF, rt.



Scheme 3. Reagents and conditions: (a) TsOH, toluene, reflux; (b) Et_3SiD, $TiCl_4$, CH_2Cl_2, −78 °C; (c) Ac_2O, Et_3 N, CH_2Cl_2, 0 °C; (d) BBr_3, CH_2Cl_2, 0 °C; see Table 1 for R residues and single reaction yields.

(1-^{2}H)-alcohols with high isotopic and enantiomeric excess starting from either L- or D-mandelic acid, respectively.

3. Experimental

3.1. General

TLC was performed on silica gel F_{254} precoated aluminum sheets (0.2 mm layer, Merck, Darmstadt, Germany); components were detected by spraying a Ceric sulfate ammonium molybdate solution, followed by heating to ca. 150 °C. Silica gel (Merck, 40–63 μm) was used for flash chromatography (FC). ^{1}H and ^{13}C NMR spectra were recorded at 400.133 and 100.613 MHz, respectively, on a Bruker Avance 400 spectrometer using a Xwin-NMR software package. Chemical shifts (δ) are given in ppm and were referenced to the signals of the solvent ($CDCl_3$, δ_H 7.27 and δ_C 77.00 ppm). ^{13}C signal multiplicities were based on APT spectra. Solvents were dried by standard methods prior to use. L-Mandelic acid, octanal, 3-phenylpropanal, phenylacetaldehyde, cyclohexane–carboxaldehyde, DIBAL-H 1 M solution in hexane and chlorotriethylsilane were purchased from Aldrich; (trifluoromethyl)trimethylsilane, was from Fluka. $LiAlD_4$ (98% atom D), used to prepare deuterotriethylsilane[10] was from Aldrich. All reagents were used as received.

3.2. Synthesis of (1*S*,2*S*)-3,3,3-trifluoro-1-phenylpropane-2,3-diol 9

To a solution of (*S*)-*O*-(*t*-butyl)dimethylsilyl mandelaldehyde **6** (11.38 g, 45.44 mmol) in dry THF (50 mL) cooled to 0 °C, (trifluoromethyl)trimethylsilane (8.0 mL, 54.52 mmol) and a catalytic amount of tetra-(*n*-butyl)ammonium fluoride (50 mg) were added and the solution was stirred at 0 °C for 45 min. The reaction mixture was diluted with AcOEt (100 mL) and washed with water (75 mL); the organic layer was separated and the aqueous layer was extracted with AcOEt (2 × 50 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a viscous yellow liquid (19.63 g). Two consecutive separations by flash column chromatography (silica gel, hexane) yielded the diastereomeric protected diols **7** (6.84 g, 36% yield) and **8** (7.17 g, 40% yield), together with an unseparated fraction (2.85 g, 16% yield).

Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.24 (s, 3H, Si*Me*$_2$*t*-Bu); −0.21 (s, 9H, $SiMe_3$); 0.04 (s, 3H, Si*Me*$_2$*t*Bu); 0.85 (s, 9H, Si*Me*$_2$*tBu*); 3.90–3.97 (m, 1H, H-2); 4.71 (d, 1H, *J* = 8.0 Hz, H-1); 7.28–7.37 (m, 5H, aromatic H). ^{13}C NMR: δ −5.05 (Si*Me*$_2$*t*Bu); −4.35 (Si*Me*$_2$*t*Bu); −0.29 ($SiMe_3$); 18.36 (*C*Me_3); 25.99 ($SiMe_2$*tBu*); 74.83 (C-1); 75.71 (q, $^2J_{C-F}$ = 28.0 Hz, C-2); 125.16 (q, $^1J_{C-F}$ = 284 Hz, CF_3); 128.28, 128.38, 128.45, 141.76 (aromatic C).

A solution of diol **7** (3.43 g, 8.7 mmol) and tetra-(*n*-butyl)ammonium fluoride (TBAF, 5.00 g, 19.2 mmol) in dry THF (9 mL) was stirred at rt for 30 min. The reaction mixture was diluted with AcOEt (100 mL) and washed with 0.1 M HCl (70 mL) and saturated NaCl solution (70 mL). The separated organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Flash column chromatography of the residue (silica gel, AcOEt–hexane 3:5) gave diol **9** as an amorphous white solid (1.77 g, 98% yield). Recrystallization from hexane gave colourless crystals, (1.54 g, 99% ee by the diester with MTPA), $[\alpha]_D = +14.1$ (*c* 1.06, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29–2.31 (m, 2H, OH); 4.21 (qdd, 1H, $J_{C-F} = J_{H3-H2} = J_{H3-OH}$ = 6.5 Hz, H-3); 4.97 (dd, 1H, J_{H2-H3} = 6.5 Hz, J_{H2-OH} = 4.2 Hz, H-2); 7.27–7.45 (m, 5H, aromatic H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 73.16 (C-1); 73.66 (q, $^2J_{C-F}$ = 30 Hz, C-2); 124.80 (q, $^1J_{C-F}$ = 281 Hz, CF_3); 127.58, 129.04, 129.26, 138.87 (aromatic C).

3.3. Synthesis of dioxolanes 14a–d. General procedure

The preparation of dioxolane **14a** is representative. A solution of diol **9** (412 mg, 2.0 mmol), octanal **13a** (0.375 mL, 2.4 mmol) and a catalytic amount of *p*-toluenesulfonic acid (1–2 mol%) in toluene (6 mL) was refluxed with azeotropic removal of water by means of a Dean-Stark apparatus until the disappearance of diol **9** (45 min., TLC monitoring). The reaction mixture was diluted with EtOAc (15 mL) and washed with saturated $NaHCO_3$ (3 × 10 mL) and saturated NaCl (10 mL). The separated organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Flash column chromatography (silica gel, AcOEt–hexane 3:97) of the residue afforded dioxolane *anti* **14a** (yellowish liquid, 114 mg, 18% yield) and dioxolane *syn* **14a** (pale yellow liquid, 456 mg, 72% yield).

anti **14a**: $[\alpha]_D = +79.1$ (*c* 1.09, EtOH); ^{1}H NMR: δ 0.90 (t, 3H, *J* = 6.8 Hz, Me); 1.31–139 (m, 8H, alkyl chain); 1.45–1.53 (m, 2H, alkyl chain); 1.72–1.78 (m, 2H, alkyl chain); 4.58–4.63 (m, 1H, H-5); 5.39 (d, 1H, *J* = 6.4 Hz, H-4); 5.65 (t, 1H, *J* = 5.2 Hz, H-2); 7.34–7.43 (m, 5H, aromatic H). ^{13}C NMR: δ 14.06 (Me); 22.63, 23.79, 29.17, 29.34, 31.71, 35.05 (CH_2 of the alkyl chain); 76.58–77.41 (overlapping with solvent, C-5); 77.83 (C-4); 107.17 (C-2); 123.22 (q, $^1J_{C-F}$ = 281 Hz, CF_3); 126.62, 128.19, 128.43, 133.05 (aromatic C).

syn **14a**: $[\alpha]_D = +101.0$ (*c* 1.00, EtOH); ^{1}H NMR: δ 0.92 (t, 3H, *J* = 6.9 Hz, Me); 1.33–1.43 (m, 8H, alkyl chain); 1.52–1.60 (m, 2H, alkyl chain); 1.88–1.93 (m, 2H, alkyl chain); 4.46–4.53 (m, 1H, H-5); 5.21 (t, 1H, *J* = 4.9 Hz, H-2); 5.26 (d, 1H, *J* = 6.6 Hz, H-4); 7.36–7.45 (m, 5H, aromatic H).^{13}C NMR: δ 14.46 (Me); 23.04, 24.17, 29.53, 29.81, 32.14, 33.84 (CH_2 of the alkyl chain); 76.54 (q, $^2J_{C-F}$ = 29 Hz, C-5); 80.03 (C-4); 106.03 (C-2); 123.42 (q, $^1J_{C-F}$ = 281 Hz, CF_3); 127.10, 128.55, 128.93, 133.27 (aromatic C).

3.4. Stereoselective reductive ring-opening reaction. Preparation of compounds 15a–d. General procedure

The preparation of hydroxy ether **15a** is representative. To a solution of a *syn*-dioxolane **14a** (167 mg, 0.53 mmol) and deuterotriethylsilane (65 mg, 0.55 mmol) in dry dichloromethane (2.5 mL) cooled at −78 °C, a 1 M solution of $TiCl_4$ in dichloromethane (0.55 mL) was added dropwise over 5 min. The reaction mixture was stirred for an additional 10 min at the same temperature and then quenched with methanol (0.25 mL). The solution was warmed to rt, diluted with AcOEt (10 mL), washed with 1 M HCl (3 × 7 mL) and saturated NaCl (7 mL). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, AcOEt–hexane 1:9) gave **15a** as a colourless liquid (150 mg, 89% yield). ^{1}H NMR: δ 0.89 (t, 3H, *J* = 6.4 Hz, Me); 1.25–1.34 (m, 10 H, alkyl chain); 1.53–1.58 (m, 2H, alkyl chain); 2.21 (br, OH); 3.28 (t, 0.95 H, *J* = 6.4 Hz, CHD); 3.37 (t, 0.05 H, *J* = 6.4 Hz, CHD); 4.12–4.18 (m, 1H, H-2); 4.49 (d, 1H, *J* = 6.4 Hz, H-3); 7.36–7.42 (m, 5H, aromatic H). ^{13}C NMR: δ 14.45 (Me); 23.02, 26.34, 29.59, 29.69, 29.86, 32.19 (CH_2 of the alkyl chain); 69.62 (t, $^1J_{C-D}$ = 21 Hz, CHD); 73.39 (q, $^2J_{C-F}$ = 29 Hz, C-2); 80.45 (C-3); 124.74 (q, $^1J_{C-F}$ = 281 Hz, CF_3); 128.25, 128.96, 129.13, 137.07 (aromatic C).

3.5. Removal of the chiral auxiliary. Synthesis of (*R*)-[1-^{2}H]-primary alcohols 17a–d. General procedure

The preparation of (*R*)-1-[^{2}H]1-octanol **17a** is representative. To a solution of compound **15a** (35 mg, 0.11 mmol) in dry dichloromethane (1 mL) cooled to 0 °C, acetic anhydride (31 μL, 0.33 mmol), triethylamine (76 μL, 0.55 mmol) and a catalytic amount of DMAP were added. The mixture was stirred for 30 min. at 0 °C, diluted with AcOEt (5 mL), washed with 1 M HCl (3 × 3 mL), saturated $NaHCO_3$ (3 × 3 mL) and saturated NaCl

(3 mL). The separated organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude acetate ester **16a** (39 mg) was dissolved in dry dichloromethane (1 mL) and the solution was cooled to 0 °C. One molar BBr_3 solution in dichloromethane (0.16 mL, 0.16 mmol) was added dropwise and the mixture was stirred for 30 min. The reaction was quenched with 15% NaOH (25 μL), diluted with water (4 mL) and extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with saturated NaCl (10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Flash column chromatography of the residue (silica gel, AcOEt–hexane 25:75) gave (*R*)-1-[^{2}H]1-octanol **17a** as a colourless liquid (10 mg, 70% yield).

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