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Synthesis and desilylation of (2*R*,3*S*)-α-methyl-α-silyl-α,β-2,3-dihydroxycarboxylic methyl esters

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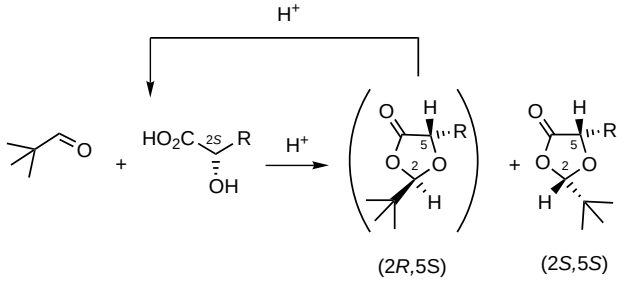
Abstract—Addition reactions of the chiral lithium (2*S*)-enolates of the (2*S*,5*S*)-2-*tert*-butyl-5-methyl-[1,3]dioxolan-4-one and (2*S*,5*S*)-2-*tert*-butyl-2,5-dimethyl-[1,3]dioxolan-4-one with linear aliphatic acylsilanes yield the corresponding (2*S*,5*R*,1′*R*)-1′-trimethylsilyl-dioxolanone alcohols. Sodium methoxide-induced removal of the acetal center at C-2 affords the corresponding methyl (2*R*,3*R*)-2,3-dihydroxy-2-methyl-3-trimethylsilyl alkanoates. The desilylation of these esters occurs with complete retention of configuration yielding the corresponding (2*R*,3*S*)-2,3-dihydroxy-2-methyl-alkanoic acids. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Chiral α-alkyl-α,β-2,3-dihydroxy acids are structural subunits of many natural products, such as macrolide-antibiotics,[1] and the acid-component of necio-alkaloids.[2] In addition, chiral dihydroxy acids derivatives are important intermediates for asymmetric synthesis. A number of useful synthetic methods for the preparation of enantiomerically pure branched hydroxy acids have been developed. However, the need for development of more efficient methods still exists. α-Alkyl-α,β-2,3-dihydroxy acids are easily prepared, without the use of chiral auxiliaries, from inexpensive, naturally occurring compounds, such as chiral α-hydroxyacids, following Seebach's synthetic principle of self-regeneration of stereocenters (SRS).[3] According to this principle, the (*S*)-α-hydroxy acids are transformed into (2*S*,5*S*)/(2*S*,5*R*) mixtures of cyclic 1,3-dioxolan-4-ones, (Scheme 1). The (2*S*,5*S*)-[1,3]dioxolan-4-ones are usually obtained as the major isomers and can be isolated in enantiomerically pure form by fractional crystallization.[3b,4] The dioxolanone is transformed into a non-racemic (2*S*)-enolate via annihilation of the original stereogenic center at C-5 with a base such as lithium diisopropylamide (LDA). The addition of the enolate to an aldehyde, or a ketone, yields a dioxolanone alcohol and removal of the auxiliary center from the dioxolanone alcohol by hydrolysis gives the chiral trisubstituted 2,3-dihydroxy acid. As an example, the reaction of an aldehyde to the (2*S*)-enolate of (2*S*,5*S*)-2-*tert*-butyl-5-methyl-[1,3]dioxolan-4-one, obtained by acetalization of the (*S*)-α-lactic acid with pivalaldehyde, yields in principle four dioxolanone alcohols (Scheme 2). The major problem of this protocol is the possible lack of stereochemical control. In principle, two stereoisomers are formed via transition states TS **I** and **II** (2*S*,5*R*,1′*S*, and 2*S*,5*R*,1′*R*, respectively). The other two stereoisomers are formed via transition states TS **III** and **IV** (2*S*,5*S*,1′*R* and 2*S*,5*S*,1′*S*). Transition states TS **I** and TS **II** are kinetically favored over TS **III** and



Scheme 1. Synthesis of diastereomeric mixtures of (2*R*,5S)- and (2*S*,5*S*)-[1,3]dioxolan-4-ones.

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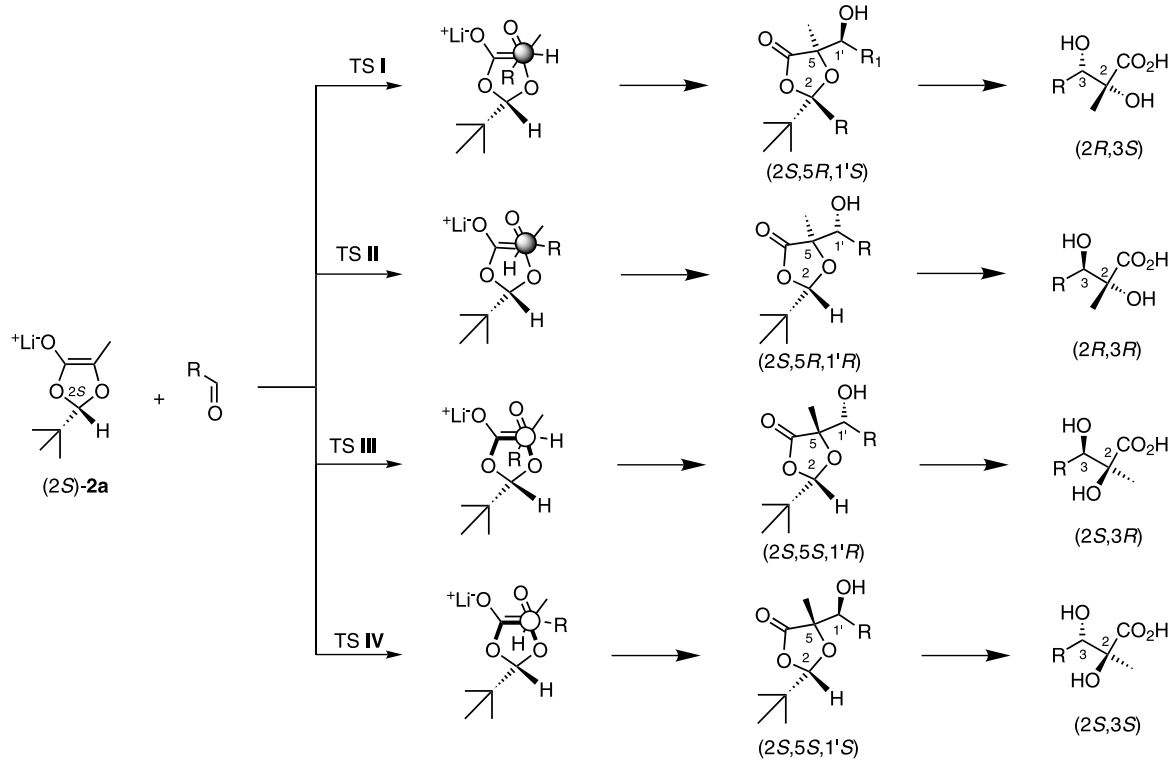


Scheme 2. Synthesis of 2,3-dihydroxy acids by hydrolysis of dioxolanone alcohols.

TS **IV** because the aldehyde approaches the enolate from the less hindered enantiotopic face which bears the hydrogen atom. Nevertheless, we have demonstrated, in a previous paper, that the addition of the (2*S*)-enolate of the (2*S*,5*S*)-2-*tert*-butyl-5-methyl-[1,3]dioxolan-4-one to aldehydes gives (2*S*,5*S*,1′*S*), (2*S*,5*R*,1′*R*), and (2*S*,5*R*,1′*S*) mixtures of dioxolanone alcohols.[5] The formation of the third (2*S*,5*S*,1′*S*)-isomer is a serious limitation for the application of this protocol because the removal of the auxiliary center of the (2*S*,5*R*,1′*S*) and (2*S*,5*S*,1′*R*) pair of dioxolanone alcohols yields mixtures of the enantiomeric (2*S*,3*S*)- and (2*R*,3*R*)-dihydroxy acids. Restrictions to the applications of the 'SRS' synthetic principle in the synthesis of macrolides and alkaloids are well documented in the literature. In fact, random diastereomeric mixtures of dioxolanone alcohols were isolated in the addition reactions of aldehydes to the (2*S*)-enolates of dioxolanones obtained by acetalization of 2-(*S*)-hydroxybutyric,[6] and 2-(*S*)-hydroxy-3-methyl-butyric[7] acids with pivalaldehyde.

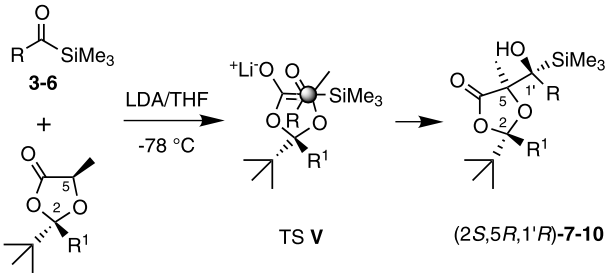
The aim of this research was the synthesis of homochiral branched 2-trimethylsilyl-2,3-dihydroxy alkanoic acids, which are highly strained structural subunits, for the synthesis of analogs of biologically active natural products. For example, isotaxoids,[8] pyrrolizidine alkaloids (indicine *N*-oxide),[7] and cephalotaxines (harringtonines),[9] bear a dihydroxy alkanoic acid appendant whose presence appears to be critical to the biological potency. The quaternary stereogenic center of the 2-trimethylsilyl-2,3-dihydroxy alkanoic acids should create additional torsional strain in the appendant, thus reducing the degree of freedom for rotation around the C2–C3 bond. Moreover, the presence of the Me_3Si substituent may favor some additional hydrophobic interaction of the molecule with the binding site of the cell. It is also worth noting that the trimethylsilyl-2,3-dihydroxy alkanoic acids can be used as precursors of the corresponding enantiomerically pure α-methyl-α,β-2,3-dihydroxy acids via desilylation protocols.

2. Results and discussion

2.1. Synthesis of 1′-trimethylsilyl-dioxolanone alcohols

Our approach to the synthesis of homochiral 2-trimethylsilyl-2,3-dihydroxy alkanoic acids used the acylsilanes **3**–**6** as the partners of (2*S*,5*S*)-2-*tert*-butyl-2-methyl-[1,3]dioxolan-4-one **1a** and (2*S*,5*S*)-2-*tert*-butyl-2,5-dimethyl-[1,3]dioxolan-4-one **1b**. The advantage of the substitution of the proton of the aldehyde with the sterically demanding Me_3Si substituent is that transition state TS **V** (Scheme 3) is favored due to the severe interaction of the Me_3Si group with both methyl and *tert*-butyl substituents of the C-2 carbon atom of the enolate. While acylsilane **3** is commercially available, compounds **4**, **5**, and **6** were prepared according to literature protocols.[10] In particular, 1-trimethylsilanyl-decan-1-one **5** was prepared for the first time. LDA-induced annihilation of the original C-5 stereogenic center of a (2*S*,5*S*)/(2*R*,5*S*) = 97:3 mixture of **1**, which was obtained from the acetalization of (*S*)-α-lactic acid with pivalaldehyde, gave the corresponding enolate [2*S*:2*R* = 97:3].[5] Similarly, the enolate of **2** [2*S*:2*R* = 93:7] was obtained from 2-*tert*-butyl-2,5-dimethyl-[1,3]dioxolan-4-one [(2*S*,5*S*)/(2*R*,5*S*) = 93:7] which was

synthesized from the acetalization of (*S*)-α-lactic acid with pinacolone.[5] The addition of the enolate of **1** to acylsilane **3** gave moderate yields of the 1′-trimethylsilyl-dioxolanone alcohol **7**. In contrast, the reaction of the more stable[11] enolate of **2** to acylsilanes **3–5**, which bear a linear aliphatic substituents such as Me, Et, and $Me(CH_2)_8$, gave compounds **8–10** in good yields (Table 1). No reaction was observed between the aromatic acylsilane **6** and the enolates of **1** and **2**. The ^1H and ^{13}C NMR spectral data of compounds **7–10** confirmed the structure of 1′-trimethylsilyl-dioxolanone alcohols. The enantiomeric excesses of **7** (e.e. = 94%) and **8–10** (e.e. = 86%) were determined by ^1H NMR analysis (400 MHz, $CDCl_3$) in the presence of the chiral shift reagent $Yt(HFC)_3$ and corresponded to the diastereomeric excess of the parent dioxolanones **1** and **2**.[12] The (2*R*,5*R*,1′*R*)-stereochemistry of compound **7** was assigned on the basis of the X-ray crystallographic studies (Fig. 1). This stereochemical result is in agreement with Heathcock's suggestion that a Zimmermann–Traxler right-angle state geometry is adopted in the addition reaction of enolates of dioxolanones to aldehydes.[13] That is, the aldehyde approaches the enolate with the hydrogen atom preferably oriented towards the acetal center (Scheme 2). However, the aliphatic substituent of linear aliphatic aldehydes does not interact significantly with the acetal hydrogen and



1: R^1 = H; **2**: R^1 = Me; **3**: R = Me; **4**: R = C_2H_5; **5**: R = C_9H_{19};
6: R = C_6H_5; **7**: R = Me, R^1 = H; **8**: R = Me, R^1 = Me;
9: R = C_2H_5, R^1 = Me; **10**: R = C_9H_{19}, R^1 = Me

Scheme 3. Synthesis of 1′-trimethylsilyl-dioxolanone alcohols.

Table 1. Synthesis of (2*S*,5*R*,1′*R*)-1′-trimethylsilyl-dioxolanone alcohols from the addition reaction of acylsilanes **3–6** to enolate (2*S*)-**1** and (2*S*)-**2**[a]

Entry	Dioxolanone	Acylsilane	Product	Yield (%)
1	(2*S*)-**1**	**3**	(2*S*,5*R*,1′*R*)-**7**	49
2	(2*S*)-**2**	**3**	(2*S*,5*R*,1′*R*)-**8**	85
3	(2*S*)-**2**	**4**	(2*S*,5*R*,1′*R*)-**9**	88
4	(2*S*)-**2**	**5**	(2*S*,5*R*,1′*R*)-**10**	81
5	(2*S*)-**1**	**6**	–	–
6	(2*S*)-**2**	**6**	–	–

[a] THF at −78°C.

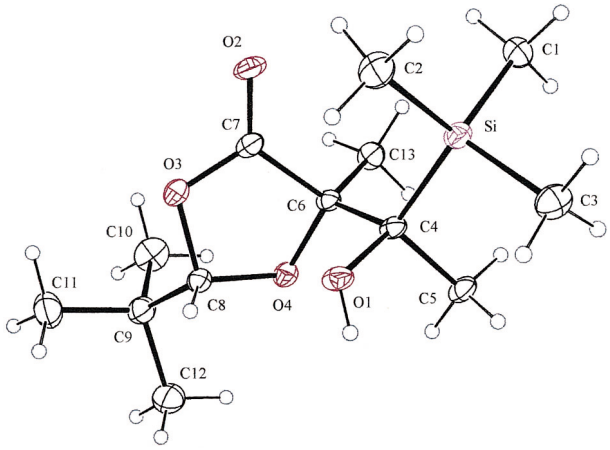
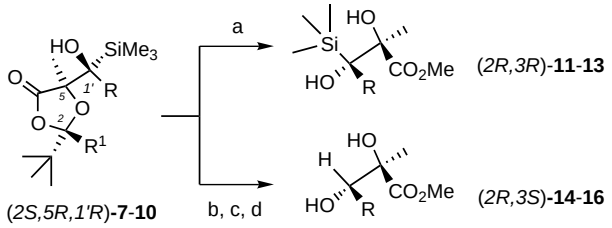


Figure 1. ORTEP drawing of compound **7** as determined by X-ray diffraction. Thermal ellipsoids are set at the 30% probability level.

the *tert*-butyl substituent of the enolate, generally leading to poor selectivity. Accordingly, the linear aliphatic group of acylsilanes **3–5** can be contained, regardless of its size, between the oxygen atom at position 3 and the C-2 carbon atom of the enolate (Scheme 3). This approach is forbidden when a ring substituent, such as the phenyl group in acylsilane **6** is present.

2.2. Desilylation of 1′-trimethylsilyl-dioxolanone alcohols

Attempted fluoride-induced protiodesilylation of 1′-trimethylsilyl dioxolanone alcohols **7–10** with HF/pyridine or tetrabutylammonium fluoride (TBAF) failed to provide the corresponding 1′-H dioxolanone alcohols. Instead, methanolysis of **7–10** at 25°C, induced by sub-stoichiometric amounts of MeO^-, gave the (2*R*,3*R*)-3-trimethylsilyl-2,3-dihydroxy methyl esters **11** and **12** in good yields, while compound **13** was obtained in moderate amounts (Scheme 4 and Table 2). Next, we attempted the protiodesilylation of the esters **11–13** in aqueous DMSO and in the presence of potassium *tert*-butoxide, according to a protocol used for the desilylation of sterically hindered α,β-dihydroxysilanes.[14] In our hands, compounds **11–13** decomposed when they were treated with a molar equivalent of *t*-BuOK in a



a: MeONa/MeOH/25 °C; b: MeONa/MeOH/60 °C;
c: H^+/H_2O; d: $SOCl_2$ MeOH

11, **14**: R = Me; **12**, **15**: R = C_2H_5; **13**, **16**: C_9H_{19}

Scheme 4. Methoxide-induced ring opening of 1′-trimethylsilyl-dioxolanone alcohols **7–10**.

Table 2. Synthesis of alkanoic esters **11–15**

Entry	Reagent	Product	Yield (%)
1	(2*S*,5*R*,1′*R*)-**7**	(2*R*,3*R*)-**11**	91
2	(2*S*,5*R*,1′*R*)-**8**	(2*R*,3*R*)-**11**	84
3	(2*S*,5*R*,1′*R*)-**9**	(2*R*,3*S*)-**12**	85
4	(2*S*,5*R*,1′*R*)-**10**	(2*R*,3*S*)-**13**	69
5	(2*S*,5*R*,1′*R*)-**7**	(2*R*,3*S*)-**14**	72
6	(2*S*,5*R*,1′*R*)-**8**	(2*R*,3*S*)-**14**	66
7	(2*S*,5*R*,1′*R*)-**9**	(2*R*,3*S*)-**15**	65
8	(2*S*,5*R*,1′*R*)-**10**	(2*R*,3*S*)-**16**	62

20:1 Me_2SO:H_2O mixture at 20°C. Instead, desilylation was successfully achieved when the esters **11–13** were treated with MeONa under forcing conditions. Consequently, we subjected all dioxolanone alcohols (2*S*,5*R*,1′*R*)-**7–10** to a one-pot MeO^- induced removal of the acetal center and the Me_3Si substituent at 65°C. The formation of amounts of the sodium salt of the free acid along with the expected methyl ester was observed during the methanolysis. For this reason, the crude reaction mixture was worked up with 2N HCl to give the free acid, which was converted into the methyl ester by treatment with $SOCl_2$ in MeOH (Scheme 4). The desilylation occurred with retention of stereochemistry, providing the (2*R*,3*S*)-2,3-dihydroxy-2-methyl-alkanoates **14–16** in moderate yields (Table 2). The formation of amounts of the corresponding (2*R*,3*R*)-isomers of **14–16** was not noticed in the crude reaction mixture by ^{1}H NMR analysis. Only small amounts of unidentified products were noticed in the case of compound **16**. The absolute configuration of (2*R*,3*S*)-**14** was assigned by comparison of the analytical data, the specific rotation value, and spectroscopic characteristics with those reported in literature.[5,15a] The stereochemistry of the methyl ester (2*R*,3*S*)-**15** was assessed by chemical correlation with the carboxylic acid (2*R*,3*S*)-**17** (see Section 4).[15b] The stereochemistry of (2*R*,3*S*)-**16** at the C-2/C-3 positions was assessed by comparison of the ^{1}H and ^{13}C NMR spectral data with those of the same compound obtained by an independent route. In fact, (2*R*,3*S*)-**16** was synthesized as the major isomer of a (2*R*,3*S*)-**16**/(2*R*,3*R*)-**16** = 1.5:1 mixture via methanolysis of a (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*) = 1.5:1 mixture of 2-*tert*-butyl-5-(1′-hydroxy-decyl)-2,5-dimethyl-[1,3]dioxolan-4-ones (see Section 4).[16] The absolute configuration of (2*R*,3*S*)-**14–16**, obtained by chemical correlation, confirmed the structure of the parent dioxolanone alcohols **7–10**, the (2*S*,5*R*,1′*R*)-stereochemistry of compound **7** being further assessed by X-ray crystallographic analysis.

3. Conclusions

We have described a simple procedure for enantioselective synthesis of branched methyl (2*R*,3*R*)-2,3-dihydroxy-2-methyl-3-trimethylsilyl- and (2*R*,3*S*)-2,3-dihydroxy-2-methyl-alkanoates via MeO^--induced methanolysis of the corresponding (2*S*,5*R*,1′*R*)-1′-trimethylsilyl-dioxolanone alcohols. These derivatives are obtained via aldol additions of aliphatic acylsilanes to the (2*S*)-enolate of the dioxolanones **1** and **2**. The aldol addition occurs only when linear aliphatic substituents are present in the acylsilane regardless of their size. Selected targets were the (2*R*,3*S*)-isomers of the methyl 2,3-dihydroxy-2-methyl-butanoate and the methyl 2,3-dihydroxy-2-methyl-pentanoate which are powerful tools in the synthesis of biologically active compounds. For example, the methyl (2*R*,3*S*)-2,3-dihydroxy-2-methyl-pentanoate is an intermediate in the total synthesis of the macrolide methynolide, the aglycone of the antibiotic methymycin.[17] Likewise, the racemic methyl (2*RS*,3*SR*)-2,3-dihydroxy-2-methyl-butanoate was used as a starting material for the synthesis of racemic citreoviral: an intermediate in the synthesis of a potent neurotoxic mycotoxin citroviridin which acts as an inhibitor of ATP synthesis.[18] Consequently, our protocol allows the synthesis of optically active (2*R*,3*S*)-citreoviral or citroviridin or of their (2*S*,3*R*)-enantiomers starting from (2*R*)-lactic acid. Additionally, the literature reports that (2*S*,3*R*)-**14** is an important component of the alkaloids germinetrin and protoveratrin C.[19]

4. Experimental

4.1. Synthesis of 2-nonyl-[1,3]dithiane

A mixture of decanal (18.0 g, 0.11 mol) and propane-[1,3]-dithiol (12.5 g, 0.11 mol) in ethyl acetate (150 mL) was heated under reflux for 4 h. The reaction mixture was concentrated under reduced pressure to give 2-nonyl-[1,3]dithiane (20 g, 0.81 mol, 74%): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.87$ (t, 3H, $J = 7.1$ Hz), 1.20–1.35 (m, 12H), 1.49 (m, 2H), 1.73 (m, 2H), 1.85 (m, 1H), 2.10 (m, 1H), 2.80–2.90 (m, 4H), 4.04 (t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 22.7, 26.1, 26.6, 29.2, 29.3, 29.4, 29.5, 30.5, 31.9, 35.5, 47.7. Anal. calcd for $C_{13}H_{26}S_2$: C, 63.35; H, 10.63. Found: C, 63.58; H, 10.46%.

4.2. Synthesis of trimethyl-(2-nonyl-[1,3]dithian-2-yl)-silane

A THF solution of *n*BuLi (2.5 M, 9.5 mL) was added at 0°C to a THF solution (30 mL) of 2-nonyl-[1,3]dithiane (2.58 g, 23.7 mmol). After 1 h Me_3SiCl (5 g, 20.3 mmol) was added. After 1 h the reaction mixture was extracted with water (15 mL), and the aqueous phase was extracted three times with diethyl ether/*n*-pentane, 1:2. The organic extracts were combined, washed with brine, dried and concentrated under reduced pressure. The residue was distilled at 143°C (0.1 Torr) to afford trimethyl-(2-nonyl-[1,3]dithian-2-yl)-silane (5.3 g, 16.6 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.19$ (s, 9H), 0.88 (t, 3H, $J = 7.5$ Hz), 1.20–1.35 (m, 12H), 1.40–1.50 (m, 2H), 1.88 (m, 1H), 2.05 (m, 1H), 2.38 (m, 2H), 2.45 (m, 2H), 3.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -2.5$, 14.1, 22.7, 23.4, 25.2, 27.7, 29.3, 29.6, 29.7, 30.3, 31.9, 37.4, 38.8. Anal. calcd for $C_{16}H_{34}S_2Si$: C, 60.31; H, 10.75. Found: C, 60.57; H, 10.86%.

4.3. Synthesis of 1-trimethylsilanyl-decan-1-one, 5

Red HgO (7 g, 32 mmol), Celite (7 g), and $BF_3{\cdot}Et_2O$ (4.1 mL, 32 mmol) were sequentially added to a THF/H_2O = 85:15 (57 mL) stirred solution of trimethyl-(2-nonyl-[1,3]dithian-2-yl)-silane (5.1 g, 16.0 mmol) at 25°C under argon. The reaction was left at 25°C for 2 h under continuous stirring. The mixture was diluted with H_2O (150 mL) and extracted with ethyl acetate. The organic phase was extracted with brine, dried, and concentrated under vacuo. Chromatography (SiO_2, *n*-hexane/EtOAc, 16:0.8) gave compound **5** (2.7 g, 11.8 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.18$ (s, 9H), 0.86 (t, 3H, $J = 7.2$ Hz), 1.20–1.30 (m, 12 H), 1.49 (m, 2H), 2.57 (t, 2H, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -3.0$, 14.3, 22.4, 22.9, 29.5, 29.6, 29.7, 29.7, 32.1, 48.8, 248.8. Anal. calcd for $C_{13}H_{28}OSi$: C, 68.35; H, 12.35. Found: C, 68.59; H, 12.46%.

4.4. General procedure for the synthesis of dioxolanone alcohols

A solution of the dioxolanone (1.0 equiv.) in THF was added to a cooled (−78°C) stirred solution of LDA (1.5 equiv.). The mixture was stirred for 15 min at −78°C and the acylsilane (1.5–2.0 equiv.) was added. Unless otherwise stated, the reaction mixture was allowed to warm to −15°C with continuous stirring over a period of 3 h. The reaction solution was quenched by the addition of saturated NH_4Cl solution (10 mL). The reaction mixture was extracted with ethyl acetate. The extracts were combined, dried, and concentrated under reduced pressure. The diastereomeric composition of the dioxolanone alcohols was established directly in the crude reaction mixture by ^{1}H NMR. The reaction mixture was subjected to purification by flash-chromatography on silica.

4.4.1. Synthesis of (2*S*,5*R*,1′*R*)-2-*tert*-butyl-5-(1-hydroxy-1-trimethylsilanyl-ethyl)-5-methyl-[1,3]dioxolan-4-one, (2*S*,5*R*,1′*R*)-7

The (2*S*,5*S*)-dioxolan-4-one **1** (*cis*/*trans* = 97:3) (0.50 g, 3.2 mmol) was reacted with 1-trimethylsilanyl-ethan-1-one **3** (0.57 g, 4.9 mmol). Chromatography of the crude reaction mixture (SiO_2, *n*-hexane/EtOAc, 14:1) gave (2*S*,5*R*,1′*R*)-**7** (0.57 g, 2.08 mmol, 65%). Mp 97–98°C; IR ($CDCl_3$): $\nu = 3530$, 2970, 1778, 1354, 1246 cm^{-1}; $[\alpha]_D^{20} = +33.9$ (*c* 1.72 in $CHCl_3$); MS *m*/*z* 259 (M^+−15), 245, 173; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.15$ (s, 9H), 0.94 (s, 9H), 1.31 (s, 3H), 1.49 (s, 3H), 5.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -1.6$ (3 Me), 21.9 (Me), 22.4 (Me), 23.5 (3 Me), 35.1 (C), 71.2 (C), 85.3 (C), 110.4 (CH), 175.6 (C). Anal. calcd for $C_{13}H_{26}O_4Si$: C, 56.90; H, 9.55. Found: C, 56.78; H, 9.60%.

4.4.2. Synthesis of (2*S*,5*R*,1′*R*)-2-*tert*-butyl-5-(1-hydroxy - 1 - trimethylsilanyl - ethyl) - 2,5 - dimethyl - [1,3]-dioxolan-4-one, (2*S*,5*R*,1′*R*)-8

The dioxolan-4-one **2** (*cis*/*trans* = 93:7) (0.80 g, 4.6 mmol) was reacted with 1-trimethylsilanyl-ethan-1-one, **3** (0.73 g, 6.3 mmol). Chromatography of the crude reaction mixture (SiO_2, *n*-hexane/EtOAc, 14:1) gave (2*S*,5*R*,1′*R*)-**8** (1.14 g, 3.93 mmol, 85%). Mp 100–102°C; IR ($CDCl_3$): $\nu = 3610$–3550, 1792, 1289, 1152 cm^{-1}; $[\alpha]_D^{20} = +17.6$ (*c* 1.14 in $CHCl_3$); MS *m*/*z* 288 (M^+), 272, 261, 189, 171; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.18$ (s, 9H), 1.01 (s, 9H), 1.32 (s, 3H), 1.49 (s, 3H), 1.62 (s, 3H), 1.78–1.80 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -1.3$, 22.3, 23.1, 25.5, 39.3, 70.7, 86.6, 115.5, 175.3. Anal. calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.51; H, 9.69%.

4.4.3. Synthesis of (2*S*,5*R*,1′*R*)-2-*tert*-butyl-5-(1-hydroxy - 1 - trimethylsilanyl - propyl) - 2,5 - dimethyl - [1,3]-dioxolan-4-one, (2*S*,5*R*,1′*R*)-9

The dioxolan-4-one **2** (0.70 g, 4.1 mmol) and 1-trimethylsilanyl-propan-1-one **4** (0.75 g, 5.8 mmol) gave after chromatography (SiO_2, *n*-hexane/EtOAc, 14:1) (2*S*,5*R*,1′*R*)-**9** (1.1 g, 3.50 mmol, 88%): mp 60–62°C; IR($CDCl_3$): $\nu = 2977$, 1783, 1291, 1251, 1150 cm^{-1}; $[\alpha]_D^{20} = +17.2$ (*c* 1.28 in $CHCl_3$); MS *m*/*z* 302 (M^+), 286, 171; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.18$ (s, 9H), 0.99 (t, 3H, $J = 7.5$ Hz), 1.00 (s, 9H), 1.52 (s, 3H), 1.62 (s, 3H), 1.72–1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -0.2$, 9.2, 22.2, 23.7, 25.4, 28.5, 39.2, 72.9, 87.1, 115.4, 175.5. Anal. calcd for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00. Found: C, 59.74; H, 9.86%.

4.4.4. Synthesis of (2*S*,5*R*,1′*R*)-2-*tert*-butyl-5-(1-hydroxy - 1 - trimethylsilanyl - decyl) - 2,5 - dimethyl - [1,3]-dioxolan-4-one, (2*S*,5*R*,1′*R*)-10

(2*S*,5*S*)-2-*tert*-Butyl-2,5-dimethyl-[1,3]dioxolan-4-one **2** (0.50 g, 2.91 mmol) and 1-trimethylsilanyl-decan-1-one **5** (0.92 g, 4.03 mmol) gave, after chromatography (SiO_2, *n*-hexane/EtOAc, 28:0.5), compound (2*S*,5*R*,1′*R*)-**10** (0.95 g, 2.36 mmol, 81%). IR (CCl_4): $\nu = 3600$, 2926, 1792, 1467, 1376, 1287, 1248, 1151 cm^{-1}; MS *m*/*z* 400 (M^+), 388, 356, 301, 285, 211, 171; $[\alpha]_D^{20} = +13.9$ (*c* 0.95 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.17$ (s, 9H), 0.86 (t, 3H, $J = 7.5$ Hz), 1.00 (s, 9H), 1.20–1.30 (m, 16 H), 1.50 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -0.2$, 14.3, 22.2, 22.9, 23.7, 24.4, 25.5, 29.5, 29.7, 29.8, 30.9, 32.1, 36.3, 39.2, 73.0, 87.1, 115.3, 175.5. Anal. calcd for $C_{22}H_{44}O_4Si$: C, 65.95; H, 11.07. Found: C, 65.77; H, 10.98%.

4.5. Synthesis of methyl (2*R*,3*R*)-2,3-dihydroxy-2-methyl-3-trimethylsilanyl-butanoate, (2*R*,3*R*)-11

A solution of MeONa (1.0 M, 1.3 mL) was added at 0°C to a stirred solution (MeOH, 2.0 mL) of (2*S*,5*R*,1′*R*)-**7** (0.28 g, 1.04 mmol). The temperature was raised to 25°C and the mixture was stirred for 6 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc. Chromatography (SiO_2, *n*-hexane/EtOAc, 13:2) gave (2*R*,3*R*)-**11** (0.21 g, 0.95 mmol, 91%). In a similar experiment, MeONa (1.0 M solution 1.3 mL) was added at 0°C to a stirred solution (MeOH, 2.0 mL) of (2*S*,5*R*,1′*R*)-**8** (0.30 g, 1.04 mmol) and the temperature was raised to 25°C and the mixture was stirred for 9 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc. Chro-

matography gave (2*R*,3*R*)-**11** (0.19 g, 0.87 mmol, 84%): Oil; IR(CCl_4): 3650–3500, 1730, 1250, 1150 cm^{-1}; $[\alpha]_D^{20} = -8.75$ (*c* 1.0 in $CDCl_3$); MS *m*/*z* 220 (M^+), 203, 187; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.07$ (s, 9H), 1.20 (s, 3H), 1.40 (s, 3H), 2.28 (b, 1H), 3.45 (b, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -1.73$, 20.8, 21.3, 52.9, 70.5, 79.7, 177.0. Anal. calcd for $C_9H_{20}O_4Si$: C, 49.06; H, 9.15. Found: C, 49.28; H, 9.26%.

4.6. Synthesis of methyl (2*R*,3*R*)-2,3-dihydroxy-2-methyl-3-trimethylsilanyl-pentanoate, (2*R*,3*R*)-12

A solution of MeONa (1.0 M, 1.3 mL) was added at 0°C to a stirred solution (MeOH, 2.0 mL) of (2*S*,5*R*,1′*R*)-**9** (0.25 g, 0.83 mmol). The temperature was raised to 25°C and the mixture was stirred for 8 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc. Chromatography (SiO_2, *n*-hexane/EtOAc, 13:2) 0.16 g (0.70 mmol, 85%) of (2*R*,3*R*)-**12**: Oil; IR(CCl_4): $\nu = 3650$–3500, 2955, 1733, 1248, 1153 cm^{-1}; $[\alpha]_D^{20} = -13.1$ (*c* 2.47 in $CHCl_3$); MS *m*/*z* 234 (M^+), 217, 200; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.14$ (s, 9H), 0.98 (t, 3H, $J = 7.6$ Hz), 1.46 (s, 3H), 1.53 (dq, 1H, $J_1 = 7.6$ Hz, $J_2 = 14.4$ Hz), 1.77 (dq, 1H, $J_1 = 7.6$ Hz, $J_2 = 14.6$ Hz), 2.30 (b, 1H), 3.39 (b, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -0.4$, 9.5, 22.3, 28.5, 52.6, 73.0, 80.1, 177.2. Anal. calcd for $C_{10}H_{22}O_4Si$: C, 51.25; H, 9.46. Found: C, 51.38; H, 9.56%.

4.7. Synthesis of methyl (2*R*,3*R*)-2,3-dihydroxy-2-methyl-3-trimethylsilanyl-dodecanoate, (2*R*,3*R*)-13

A solution of MeONa (1.0 M, 0.16 mL) was added at 0°C under nitrogen to a stirred solution (MeOH, 2.0 mL) of (2*S*,5*R*,1′*R*)-**10** (0.32 g, 0.80 mmol). The temperature was raised to 25°C and the mixture was stirred for 12 h. A further 0.16 mL of the solution of MeONa was added and the reaction was stirred for 12 h at this temperature. The reaction mixture was poured into water (10 mL) and extracted with EtOAc. Chromatography (SiO_2, *n*-hexane/EtOAc, 13:2) gave (2*R*,3*R*)-**13** (0.18 g, 0.54 mmol, 67%): Oil; IR(CCl_4): $\nu = 3436$, 2925, 1645, 1246 cm^{-1}; $[\alpha]_D^{20} = -9.6$ (*c* 0.60 in $CHCl_3$); MS *m*/*z* 332 (M^+), 315; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.14$ (s, 3H), 0.88 (t, 3H, $J = 7.0$ Hz), 1.20–1.30 (m, 12H), 1.36–1.48 (b, 4H), 1.46 (s, 3H), 2.28–2.34 (b, 1H), 3.38–3.40 (b, 1H) 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 0.08$, 14.5, 22.7, 23.1, 25.2, 29.7, 29.9, 30.0, 31.3, 32.3, 36.7, 53.0, 73.2, 80.5, 177.2. Anal. calcd for $C_{17}H_{36}O_4Si$: C, 61.40; H, 10.91. Found: C, 61.81, H, 10.84%.

4.8. Synthesis of methyl (2*R*,3*S*)-2,3-dihydroxy-2-methyl-butanoate, (2*R*,3*S*)-14

A solution of MeONa (1.0 M, 0.85 mL) was added to a stirred solution of (2*S*,5*R*,1′*R*)-**8** (0.29 g, 1.0 mmol) in methanol (1.5 mL). The solution was heated under stirring at 65°C for 3 h. Aqueous NaOH solution (2 M, 0.5 mL) was added at 65°C and left at this temperature for 30 min. Water (10 mL) was added to the reaction solution and extracted with EtOAc. The aqueous solution was acidified with a 2N solution of HCl and evaporated under vacuum. The residue was extracted with acetone (25 mL), filtered and evaporated. This residue was dissolved in MeOH (5 mL) and $SOCl_2$ (0.14 g, 1.20 mmol) were added at 25°C under argon. After 20 h the solvent was removed under vacuum and the residue was chromatographed (SiO_2, *n*-pentane/EtOAc, 2:3) to yield (2*R*,3*S*)-**14** (0.098 g, 0.66 mmol, 66%). In an identical experiment (2*S*,5*R*,1′*R*)-**7** (0.27 g, 1.0 mmol) gave (2*R*,3*S*)-**14** (0.11 g, 0.72 mmol, 72%): $[\alpha]_D^{20} = -1.0$ (*c* 1.2 in $CDCl_3$); the literature[14a] $[\alpha]_D^{23}$ value of the enantiomer (2*S*,3*R*)-**14** is +1.0 (*c* 6.67 in $CDCl_3$); IR ($CDCl_3$): $\nu = 3450$, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$ (d, 3H, $J = 6.8$ Hz), 1.32 (s, 3H), 2.25 (b, 1H), 3.40 (b, 1H), 3.81 (s, 3H), 3.95 (q, 1H); the literature ^1H NMR ($CDCl_3$):[14a] $\delta = 1.23$, 1.33, 2.94, 3.82, 3.96; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.6$, 21.6, 53.0, 71.7, 77.5, 176.5; the literature ^{13}C NMR ($CDCl_3$):[14a] $\delta = 16.2$, 21.3, 52.6, 71.5, 77.4, 176.5. Anal. calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.71; H, 8.18%.

4.9. Synthesis of methyl (2*R*,3*S*)-2,3-dihydroxy-2-methyl-pentanoate, (2*R*,3*S*)-15

MeONa (0.90 mL of a 1.0 M solution) was added to a stirred MeOH solution (1.5 mL) of (2*S*,5*R*,1′*R*)-**9** (0.35 g, 1.16 mmol). The solution was heated under stirring at 65°C for 3 h. NaOH (0.5 mL of a 2 M solution) was added at 65°C and left at this temperature for 30 min. Water (10 mL) was added to the reaction solution and extracted with EtOAc. The aqueous solution was acidified with a 2N solution of HCl and evaporated under vacuum. The residue was extracted with 25 mL of aceton, filtered and evaporated. This residue was dissolved in 5 mL of MeOH and 0.16 g (1.34 mmol) of $SOCl_2$ were added at 25°C under argon. After 20 h the solvent was removed under vacuum and the residue was chromatographed (SiO_2, *n*-pentane/EtOAc, 2:3) to yield 0.12 g of (2*R*,3*S*)-**15** (0.75 mmol, 65%): $[\alpha]_D^{20} = -19.9$ (*c* 1.38 in $CDCl_3$); IR (CCl_4): $\nu = 3570$, 2969, 1731.8, 1456, 1264 cm^{-1}; MS *m*/*z* 162 (M^+), 145, 103, 86; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.99$ (t, 3H, $J = 7.3$ Hz), 1.30 (s, 3H), 1.37 (m, 1 H, $J = 14.2$ Hz), 1.63 (m, 1H), 2.23–2.24 (b, 1H), 3.51–3.55 (b, 1H), 3.59 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.7$, 21.9, 23.4, 53.2, 77.0, 77.8, 177.1. Anal. calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 52.03; H, 8.56%.

4.10. Synthesis of methyl (2*R*,3*S*)-2,3-Dihydroxy-2-methyl-dodecanoate, (2*R*,3*S*)-16:

A solution of MeONa (1.0 M, 0.90 mL) was added to a stirred solution of (2*S*,5*R*,1′*R*)-**10** (0.75 g, 1.8 mmol) in methanol (9 mL). The solution was heated at 65°C and 0.9, 0.2 and 0.2 mL of the MeONa solution were sequentially added after 10 min, 2 and 3 h, respectively. Aqueous NaOH solution (2 M, 5 mL) was added at 65°C after 20 h and the mixture was stirred at this temperature for 30 h. Water (20 mL) was added to the reaction solution and extracted with a 1:1.5:1 mixture of *n*-pentane/Et_2O/EtOAc. The aqueous solution was acidified with a 2N aqueous HCl solution and evapo-

rated. The residue was extracted with acetone (25 mL) filtered and evaporated to yield 0.26 g of crude material. This residue was dissolved in MeOH (5 mL) and $SOCl_2$ (0.07 mL) was added at 25°C under argon. After 20 h the solvent was removed under vacuo and the residue (0.23 g) was chromatographed (SiO_2, *n*-pentane/EtOAc, 12:3) to yield (2*R*,3*S*)-**16** (0.29 g, 1.11 mmol, 62%): $[\alpha]_D^{20}=-25.0$ (*c* 1.0 in $CHCl_3$); MS *m*/*z* 260 (M^+), 243, 201, 183, 104; IR (CCl_4): $\nu=3400$, 2924, 2851, 1749, 1466, 1236, 1116 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.87$ (t, 3H, $J=6.8$ Hz), 1.20–1.90 (m, 17H), 1.34 (s, 3H), 3.70 (d, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.3$, 22.0, 22.9, 26.1, 29.5, 29.8 (3 CH_2), 30.5, 32.1, 53.3, 75.7, 77.7, 179.1. Anal. calcd for $C_{14}H_{28}O_4$: C, 64.58; H, 10.84. Found: C, 64.81, H, 10.76%.

4.11. MeO^--induced methanolysis of a (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*)=1.5:1 mixture of 2-*tert*-butyl-5-(1′-hydroxy-decyl)-2,5-dimethyl-[1,3]dioxolan-4-ones

A solution of MeONa (1.0 M, 0.50 mL) was added to a stirred MeOH solution (3.0 mL) of a (2*S*,5*R*,1′*S*)/(2*S*,5*R*,1′*R*)=1.5:1 mixture of 2-(*tert*-butyl)-5-(1′-hydroxydecyl)-5-methyl-[1,3]dioxolan-4-ones[5] (0.25 g, 0.8 mmol). The mixture was stirred at 20°C for 3 h. The crude reaction mixture was diluted with saturated NH_4Cl and extracted with ethyl acetate. The extract was dried and concentrated under reduced pressure. Chromatography (SiO_2, *n*-pentane/EtOAc, 20:1) gave (2*R*,3*S*)/(2*R*,3*R*)=1:5:1 mixture of compounds **16** (0.201 g, 0.195 g, 0.75 mmol, 94%): ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.87$ [t, 3H, of (2*R*,3*S*)-**16** and (2*R*,3*R*)-**16**, $J=6.8$ Hz], 1.20–1.90 [m, 17H, of (2*R*,3*S*)-**16** and (2*R*,3*R*)-**16**)], 1.34 [s, 3H of (2*R*,3*S*)-**16**], 1.43 [s, 3H of (2*R*,3*R*)-**16**], 3.53 [d, 1H of (2*R*,3*R*)-**16**], 3.70 [d, 1H of (2*R*,3*S*)-**16**], 3.78 [s, 3H of (2*R*,3*R*)-**16**], 3.81 [s, 3H of (2*R*,3*S*)-**16**].

4.12. Synthesis of (2*R*,3*S*)-2,3-dihydroxy-2-methyl-pentanoic acid, (2*R*,3*S*)-17

A solution of MeONa in MeOH (1.0 M, 3.6 mL) was added to a stirred methanolic solution of (2*S*,5*R*,1′*R*)-**8** (0.16 g, 0.53 mmol) at 25°C. After 4 h at 60°C, water (0.5 mL) was added and the reaction mixture was left at this temperature for an additional hour. The solvent was removed under reduced pressure, the residue was dissolved in 5.0 mL of water and extracted with ethyl ether. The aqueous solution was acidified with 1N HCl and extracted with ethyl acetate. The extract was dried and concentrated under reduced pressure to give (2*R*,3*S*)-**17** (0.055 g, 0.37 mmol, 70%). IR (CCl_4): $\nu=$ 3650–3500, 2928, 1714 cm^{-1}; $[\alpha]_D^{20}=-27.0$ (*c* 0.75 in D_2O). Literature[5,14b] $[\alpha]_D^{20}=-27.1$; MS *m*/*z* 148 (M^+), 90; ^1H NMR (400 MHz, D_2O): $\delta=0.79$ (t, 3H, $J=7.9$ Hz), 1.10–1.25 (m, 1H), 1.17 (s, 3H), 1.48 (m, 1H, $J_1=7.9$ Hz, $J_2=2.1$ Hz), 3.48 (m, 1H, CH, $J_1=10.6$ Hz, $J_2=2.1$ Hz). Literature:[5] $\delta=0.77$, 1.05–1.20, 1.15, 1.40–1.52, 3.46; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=10.3$, 21.5, 22.5, 77.2, 78.1, 179.0. Anal. calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.48; H, 8.26%.

4.13. X-Ray data collection and structure refinement

A suitable crystal of compound **7** was mounted on a glass fiber and placed in the low temperature nitrogen stream. The X-ray intensity data were measured on a Bruker-AXS SMART2000 CCD-based diffractometer at low temperature (230 K) using graphite monochromated Mo Kα radiation. The initial cell parameters and an orientation matrix were obtained from least-squares refinement on reflections measured in three different sets of 20 frames each, in the range $-15<\vartheta<15°$. The intensity data comprising a hemisphere were collected using the ω-scan technique with frame width set at 0.3°, 20 s exposures/frame and sample-detector distance kept at 5.0 cm. The first 50 frames were remeasured at the end of data collection to monitor decay. The collected frames were then processed for integration by SAINT software package and an empirical absorption correction was applied by SADABS.[20] The structure was solved by direct methods (SIR-97)[21] and refined by full-matrix least-squares on F_o^2 using SHELXTL.[22] Anisotropic displacement parameters were assigned to all non-hydrogen atoms in the structure. The hydrogen atom on the oxygen was experimentally located while the others were placed on idealized positions. The absolute configuration was independently determined on the basis of the diffraction data with a good level of significance (Flack parameter 0.0(2)). Crystallographic data and structure refinement parameters are presented in Table 3.

The crystallographic data for **7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 182416. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Table 3. Crystallographic data for compound **7**

Empirical formula	$C_{13}H_{26}O_4Si$
FW	274.43
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	*P* 1 (No. 1)
a (Å)	6.389(1)
b (Å)	6.423(1)
c (Å)	10.945(2)
α (°)	93.739(5)
β (°)	109.950(2)
γ (°)	115.424(4)
Volume ($Å^3$)	396.3(1)
Z	1
Calculated density (g cm^{-1})	1.150
Absorption coefficient (mm^{-1})	0.153
Unique data/parameters	3772/177
Goodness of fit on F^2	1.025
$R_1(F_o)$ [$I>2\sigma(I)$[a]]	0.0631
$wR_2(F_o^2)$ (all data)[b]	0.1487

[a] $R(F_o)=\Sigma||F_o|-|F_c||/\Sigma|F_o|$.
[b] $wR_2(F_o^2)=[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

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12. In particular, the addition of $Yt(hfc)_3$ (8.0 mg) to of **7**–**10** (20 mg) shifted the C2–Me signal of the (2*S*,5*R*,1′*R*)-isomer at lower field (0.02 ppm) with respect to that of the (2*R*,5*S*,1′*S*)-enantiomer.
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