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Revision of stereochemical assignments of (2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-methanol

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Abstract—Opposite signs of specific rotation are reported in the literature for (4*S*,5*S*)-(2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-methanol. The correct assignment was made by unambiguous synthesis of the title compound via the reaction of (*S*)-*O*-TBS-mandelic aldehyde with vinyl magnesium chloride, separation of diastereomeric (1*S*,2*S*)- and (1*S*,2*R*)-1-phenyl-but-3-ene-1,2-diols, and transformation of (1*S*,2*S*)-diol into authentic (4*S*,5*S*)-(2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-methanol.

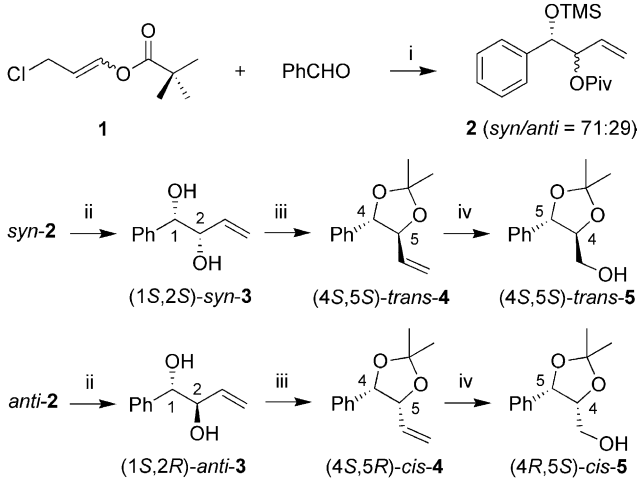
1. Introduction

In the field of asymmetric synthesis, the assignment of absolute configurations to newly formed stereogenic centres is often based, besides on physical methods, on direct chemical correlation: A chiral molecule produced in its enantiopure or enantioenriched form is transformed into one or the other of the antipodes of a reference substance by using reactions, which do not affect the stereogenic centres. If the specific rotation of the reference molecule is known, the sign of rotation represents an experimental criterion for the assignment of absolute configurations. However risks are associated with the use of a simple polarimetric analysis, particularly when the sign of rotation shows a strong solvent, concentration, wavelength or temperature dependence, when specific rotation is too small and a trace impurity with a high specific rotation may overwhelm the sample rotation, and, finally, when an incorrect assignment is reported in the literature.

A representative case recently occurred to us while developing an asymmetric catalytic entry to alk-1-ene-3,4-diols.[1]

2. Results and discussion

When 3-chloro propenyl pivaloate **1** is reacted with an in situ generated Salen/Cr(II) species in the Fürstner version[2] of the Nozaki–Hiyama–Kishi reaction,[3] a heterosubstituted allylic chromium(III) is formed, which adds to benzaldehyde to give enantiomerically enriched *syn*-**2** and *anti*-**2** in the 71:29 ratio.[1] Enantiomeric excesses of *syn*-**2** (64%) and *anti*-**2** (43%) were measured, after removal of pivaloate and trimethylsilyl groups ($LiAlH_4$, THF) and derivatisation of *syn*-**3** and *anti*-**3** diols as dioxolanes *trans*-**4** and *cis*-**4**, respectively, by chiral GC analysis using a cyclodextrin Megadex 5 column. The overall process is summarised in Scheme 1.



Scheme 1. Reagents and conditions: (i) $CrCl_2$ (10%)/Mn, (*R*,*R*)-Salen (20%), Et_3N (40%), $TMSCl/CH_3CN$; (ii) $LiAlH_4$, THF; (iii) $Me_2C(OMe)_2$, CH_2Cl_2, H^+; (iv) O_3, CH_2Cl_2 then $LiAlH_4$, THF.

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Since the specific rotations for both enantiomers of *anti*-**3** are known,[4] we were able to unambiguously assign the (1*S*,2*R*) absolute configuration to the major isomer of *anti*-**2** obtained by the (*R*,*R*)-Salen/Cr(II) catalysed reaction. Unfortunately, no data for *syn*-**3** diols were found in the literature.

As even specific rotations of *cis*-**4** and *trans*-**4** are not known, in order to unequivocally determine the absolute configurations and the sense of asymmetric induction of the above reported Salen/Cr(II)-based catalytic cycle, we subjected **4** to reductive ozonolysis (Scheme 1), since specific rotations of the four steroisomers of **5** (Fig. 1) are known (Table 1).[5–10]

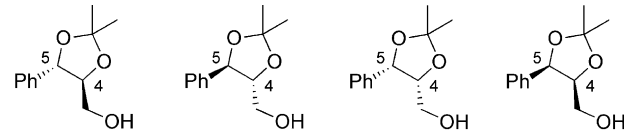


Figure 1.

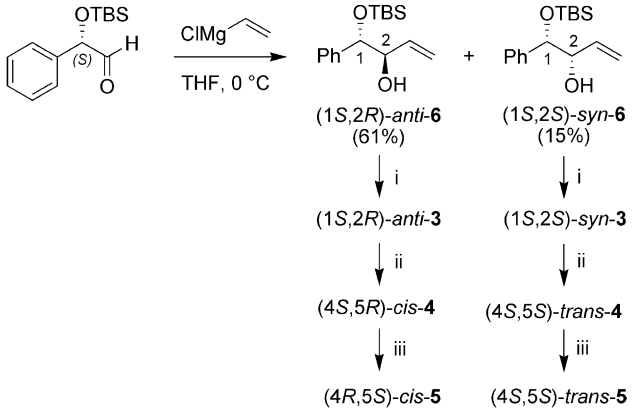
Table 1. Specific rotation values of the four stereoisomers of acetonide **5**

Stereoisomer	$[\alpha]_D^{20}$	Reference
(4*S*,5*S*)-*trans*-**5**	−19.5 (*c* 3.1, CH_2Cl_2)	5
	+24 (*c* 0.36, CH_2Cl_2)	6
	+32.7 (*c* 1.2, EtOH)	7
(4*R*,5*R*)-*trans*-**5**	+19.4 (*c* 3.0, CH_2Cl_2)	5
	+19.5 (*c* 2.9, CH_2Cl_2)	8
(4*R*,5*S*)-*cis*-**5**	+80 (*c* 2.73, CH_2Cl_2)	6
(4*S*,5*R*)-*cis*-**5**	−84 (*c* 3.7, MeOH)	9
	−112.3 (*c* 1.3, $CHCl_3$)	7
	−112 (*c* 1.2, $CHCl_3$)	10

Unfortunately, as apparent from data reported in Table 1, no unambiguous stereoassignment was possible for the major isomer of *trans*-**5** obtained by us, which shows $[\alpha]_D^{20}$ +20 (*c* 0.8, $CHCl_3$), since opposite specific rotation signs are reported in the literature.[5–8]

If data reported by Refs. 5 and 8 were correct, the major *syn*-product in our reaction should correspond to the (1*R*,2*R*)-diol. These results should imply a stereodivergent π-face selectivity of the intermediate allyl Cr(III) species, which preferentially should attack either the aldehyde *re* face when the *syn*-selective reaction channel is followed, or the *si* face, when *anti*-adducts are formed. Conversely, if data reported by Refs. 6 and 7 were correct, the major *syn*-diol in our reaction should correspond to the (1*S*,2*S*)-isomer.

To definitely ascertain the right assignments, we carried out a synthesis of authentic (4*R*,5*S*)-*cis*-**5** and (4*S*,5*S*-*trans*)-**5**, as outlined in Scheme 2.



Scheme 2. Reagents and conditions: (i) TBAF, THF; (ii) $Me_2C(OMe)_2$, H^+; (iii) O_3 then $LiAlH_4$.

(*S*)-Mandelic aldehyde, protected as *tert*-butyldimethylsilyl (TBS) ether, is reacted with vinyl magnesium chloride to give alcohols (1*S*,2*R*)-*anti*-**6** and (1*S*,2*S*)-*syn*-**6** in 76% overall yield and in the 80:20 *anti*/*syn* ratio. Protodesilylation of **6** (TBAF) afforded (1*S*,2*R*)-*anti*-**3** and (1*S*,2*S*)-*syn*-**3**, respectively; *anti*-**3** and *syn*-**3** were identified by comparison of spectroscopic data with authentic racemic compounds synthesised in a previous work.[11] Protection of **3** as the acetonides (4*S*,5*R*)-*cis*-**4** and (4*S*,5*S*)-*trans*-**4** followed by reductive ozonisation, allowed us to isolate pure (4*R*,5*S*)-*cis*-**5** and (4*S*,5*S*)-*trans*-**5**.

Authentic (4*S*,5*S*)-*trans*-**5** shows an $[\alpha]_D^{20}$ +15.6 (*c* 0.36, CH_2Cl_2) and $[\alpha]_D^{20}$ +14.7 (*c* 3.05, CH_2Cl_2); thus, we *established* that (i) (4*S*,5*S*)-(2,2-dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-methanol **5** *does correspond to the dextrorotatory enantiomer*, and (ii) consequently, *syn*-**2** coming from the (*R*,*R*)-Salen/Cr(II)-catalysed reaction does correspond to the (1*S*,2*S*) isomer.

For the sake of clarity, all the specific rotations of products **3**–**6** are collected in Table 2.

Table 2. Specific rotation values of products **3**–**6**

Stereoisomer	$[\alpha]_D^{20}$[a]
(1*S*,2*R*)-*anti*-**6**	+66 (*c* 1.46, $CHCl_3$)
(1*S*,2*S*)-*syn*-**6**	+43 (*c* 1.44, $CHCl_3$)
(1*S*,2*R*)-*anti*-**3**	+73 (*c* 1.26, $CHCl_3$)
(1*S*,2*S*)-*syn*-**3**	+2 (*c* 0.71, $CHCl_3$)
(4*S*,5*R*)-*cis*-**4**	+43 (*c* 1.56, $CHCl_3$)
(4*S*,5*S*)-*trans*-**4**	+36 (*c* 1.61, $CHCl_3$)
(4*R*,5*S*)-*cis*-**5**	+96 (*c* 2.89, CH_2Cl_2)
(4*S*,5*S*)-*trans*-**5**	+16 (*c* 0.36, CH_2Cl_2)
	+15 (*c* 3.05, CH_2Cl_2)
	+19 (*c* 0.81, $CHCl_3$)

[a] The relative errors were in the range ±3–5% ($n = 10$).

We believe that correcting literature stereoassignments has the major importance of avoiding later misunderstandings of the stereochemical outcome of an asymmetric transformation,[12] as would happen if a wrong specific rotation value were used to identify stereoproducts.

3. Experimental

The purity of all title compounds was established to be >97% by inspection of ^{1}H and ^{13}C NMR spectra, GC–MS analyses and elemental analysis (±0.4% for C and H). Optical rotations were measured on a Perkin–Elmer 241 polarimeter, using a 10 mm cell path length.

3.1. 1-Phenyl-1-(*tert*-butyldimethylsilyl)-but-3-ene-2-ol 6

Vinylmagnesium chloride (1.0 M in THF, 6 mL, 6 mmol) was added at 0 °C to a solution of (*S*)-*O*-*tert*-butyldimethylsilyl mandelic aldehyde (1.0 g, 4 mmol) in THF (8 mL), and the reaction mixture stirred at 0 °C for 3 h. The reaction was quenched by the addition of aq $NaHCO_3$ and the organic layer extracted with ether. The combined organic layers were dried over Na_2SO_4 and evaporated at reduced pressure. Purification by flash chromatography on SiO_2 (cyclohexane/ethyl acetate 95:5) afforded 0.167 g of *syn*-**6** (0.60 mmol, 15%) and 0.675 g of *anti*-**6** (2.43 mmol, 61%).

3.1.1. (1*S*,2*R*)-*anti*-6. ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.18 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 4.14 (ddt, $J = 1.2/4.8/5.6$ Hz, 1H), 4.61 (d, $J = 4.8$ Hz, 1H), 5.11 (dt, $J = 1.2/10.6$ Hz, 1H), 5.18 (dt, $J = 1.2/17.2$ Hz, 1H), 5.76 (ddd, $J = 5.6/10.6/17.2$ Hz, 1H), 7.20–7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.6, 18.1, 25.7, 77.3, 78.2, 116.6, 127.0, 127.6, 127.9, 136.6, 140.8.

3.1.2. (1*S*,2*S*)-*syn*-6. ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.19 (s, 3H), 0.05 (s, 3H), 0.90 (s, 9H), 4.12 (ddt, $J = 1.3/5.5/6.8$ Hz, 1H), 4.44 (d, $J = 6.8$ Hz, 1H), 5.10 (dt, $J = 1.4/10.6$ Hz, 1H), 5.21 (dt, $J = 1.4/17.3$ Hz, 1H), 5.68 (ddd, $J = 5.5/10.6/17.3$ Hz, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.1, −4.6, 18.1, 25.8, 77.3, 79.1, 116.5, 127.2, 127.8, 128.0, 136.2, 140.9.

3.2. (1*S*,2*R*)-1-Phenyl-but-3-ene-1,2-diol *anti*-3

Tetrabutylammonium fluoride (TBAF, 0.347 g, 1.1 mmol) was added at 0 °C to a solution of (1*S*,2*R*)-*anti*-**6** (0.257 g, 0.93 mmol) in THF (2 mL). After being stirred for 2 h at rt, the reaction was quenched with water and the organic layer extracted with ether. The combined organic layers were dried over Na_2SO_4 and evaporated at reduced pressure. Purification by flash chromatography on SiO_2 (cyclohexane/ethyl acetate 70:30) afforded 0.133 g of (1*S*,2*R*)-*anti*-**3** (0.81 mmol, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (ddt, $J = 1.2/4.9/6.1$ Hz, 1H), 4.78 (d, $J = 4.9$ Hz, 1H), 5.24 (dt, $J = 1.2/10.4$ Hz, 1H), 5.30 (dt, $J = 1.3/17.3$ Hz, 1H), 5.83 (ddd, $J = 6.1/10.4/17.3$ Hz, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.3, 76.5, 117.5, 126.6, 127.6, 128.1, 135.5, 139.8.

3.3. (1*S*,2*S*)-1-Phenyl-but-3-ene-1,2-diol *syn*-3

The analogous reaction of TBAF with (1*S*,2*S*)-*syn*-**6** (0.153 g, 0.55 mmol), afforded (1*S*,2*S*)-*syn*-**3** in 95% yield (0.087 g, 0.52 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.27 (ddt, $J = 1.5/5.5/6.9$ Hz, 1H), 4.52 (d, $J = 6.9$ Hz, 1H), 5.16 (dt, $J = 1.4/10.6$ Hz, 1H), 5.25 (dt, $J = 1.4/17.3$ Hz, 1H), 5.75 (ddd, J = 5.3/10.4/17.3 Hz, 1H), 7.26–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.9, 77.5, 116.9, 127.0, 128.0, 128.3, 136.3, 140.2.

3.4. (4*S*,5*R*)-2,2-Dimethyl-4-phenyl-5-ethenyl[1,3]dioxolane *cis*-4

2,2-Dimethoxy-propane (0.17 mL, 1.4 mmol) was added at rt to a solution of (1*S*,2*R*)-*anti*-**3** (0.113 g, 0.69 mmol) in CH_2Cl_2 (3 mL), in the presence of a catalytic amount of Amberlyst®-15H. The reaction mixture was stirred at rt overnight, filtered through a small pad of Celite® and the organic layer evaporated at reduced pressure. Purification by flash chromatography on SiO_2 (cyclohexane/ethyl acetate 95:5) afforded 0.138 g of (4*S*,5*R*)-*cis*-**4** (0.68 mmol, 99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (s, 3H), 1.69 (s, 3H), 4.82 (br t, $J = 6.7$ Hz, 1H), 4.94–5.04 (m, 1H), 5.22 (dd, $J = 3.3/17.4$ Hz, 1H), 5.30 (d, $J = 7.2$ Hz, 1H), 5.26–5.41 (m, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.9, 27.3, 80.1, 80.6, 108.8, 117.8, 126.8, 127.6, 128.0, 134.9, 137.4.

3.5. (4*S*,5*S*)-2,2-Dimethyl-4-phenyl-5-ethenyl[1,3]dioxolane *trans*-4

By applying the same procedure to (1*S*,2*S*)-*syn*-**3** (0.062 g, 0.38 mmol), we obtained (4*S*,5*S*)-*trans*-**4** in 97% yield (0.075 g, 0.37 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.56 (s, 3H), 1.60 (s, 3H), 4.20 (ddt, $J = 1.1/7.0/8.4$ Hz, 1H), 4.67 (d, $J = 8.4$ Hz, 1H), 5.26 (dt, $J = 1.0/10.0$ Hz, 1H), 5.27 (dt, $J = 1.0/17.5$ Hz, 1H), 5.90 (ddd, $J = 6.9/9.9/17.5$ Hz, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.00, 27.07, 82.9, 84.6, 109.2, 119.2, 126.4, 128.1, 128.4, 133.8, 137.1.

3.6. (4*R*,5*S*)-(2,2-Dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-methanol *cis*-5

A solution of (4*S*,5*R*)-*cis*-**4** (0.138 g, 0.68 mmol) in CH_2Cl_2 (15 mL) was allowed to react with ozone for 30 min at −78 °C. The reaction mixture was allowed to reach rt while argon was bubbled into the solution to remove excess ozone. The solvent was evaporated at reduced pressure and the residue redissolved in anhydrous THF (5 mL) after which $LiAlH_4$ (1.0 M in THF, 0.14 mL, 1.44 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 2 h, quenched with aq $NaHCO_3$, filtered on Celite® and extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated at reduced pressure. Purification by flash chromatography on SiO_2 (cyclohexane/ethyl acetate 80:20) afforded 0.095 g of (4*R*,5*S*)-*cis*-**5** (0.46 mmol, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 3H), 1.65

(s, 3H), 3.12 (dd, $J = 4.6/11.6$ Hz, 1H), 3.25 (dd, $J = 8.0/11.6$ Hz, 1H), 4.47 (ddd, $J = 4.6/6.9/8.0$ Hz, 1H), 5.33 (d, $J = 6.9$ Hz, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 27.4, 62.7, 78.2, 78.8, 108.8, 126.2, 128.0, 128.3, 136.2.

3.7. (4*S*,5*S*)-(2,2-Dimethyl-5-phenyl-[1,3]dioxolan-4-yl)-methanol *trans*-5

The same reductive ozonisation reported above, was applied to (4*S*,5*S*)-*trans*-**4** (0.074 g, 0.36 mmol), to afford (4*S*,5*S*)-*trans*-**5** in 61% yield (0.045 g, 0.22 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.60 (s, 3H), 3.66 (dd, $J = 4.6/13.1$ Hz, 1H), 3.84–3.92 (m, 2H), 4.90 (d, $J = 8.2$ Hz, 1H), 7.29–7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.06, 27.11, 60.3, 78.6, 83.6, 109.3, 126.5, 128.3, 128.6, 137.6.

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