## SUPPORTING INFORMATION

# On the Enolization of Chiral α-Silyloxy Ketones with Dicyclohexylchloroborane. Application to Stereoselective Aldol Reactions

Marta Galobardes, Miguel Gascón, Marisa Mena, Pedro Romea,* Fèlix Urpí,* Jaume Vilarrasa

**(1*R*,2*R*,4*S*)-4-*tert*-Butyldimethylsilyloxy-1-hydroxy-2-methyl-1-phenyl-3-pentanone (5a)**

Colourless oil. $\mathbf{R_f}$ (hexanes/EtOAc 9:1) = 0.15. $\mathbf{[\alpha]_D}$ = +4.2 (*c* = 1.0, $CHCl_3$). **IR** (film): υ 3500, 1713 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.34–7.30 (4H, m, ArH), 7.26–7.21 (1H, m, ArH), 5.03 (1H, d, *J* = 3.7, PhC<u>H</u>OH), 4.14 (1H, q, *J* = 6.9, C<u>H</u>OTBS), 3.37 (1H, qd, *J* = 7.2, *J* = 3.7, COC<u>H</u>$CH_3$CHOH), 1.27 (3H, d, *J* = 6.9, C<u>H</u>$_3$CHOTBS), 1.05 (3H, d, *J* = 7.2, COCHC<u>H</u>$_3$CHOH), 0.90 (9H, s, SiC$(CH_3)_3$), 0.08 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 218.7, 141.7, 128.2, 127.2, 125.9, 74.6, 72.8, 46.9, 25.7, 21.0, 18.0, 10.4, –4.7, –5.0. **HRMS (+FAB)**: *m/z* $[M+H]^+$ found 323.2045, $C_{18}H_{31}O_3Si$ requires 323.2042.

**(2*S*,4*R*,5*S*,6*E*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4-methyl-6-octen-3-one (5b)**

Yellowish oil. $\mathbf{R_f}$ (hexanes/EtOAc 9:1) = 0.2. $\mathbf{[\alpha]_D}$ = –6.3 (*c* = 1.3, $CHCl_3$). **IR** (film): υ 3475, 1709, 1640 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.72 (1H, dqd, *J* = 15.7, *J* = 6.5, *J* = 1.2, HC=C<u>H</u>$CH_3$), 5.44 (1H, ddq, *J* = 15.7, *J* = 6.5, *J* = 1.7, <u>H</u>C=CH$CH_3$), 4.36–4.32 (1H, m, C<u>H</u>OH), 4.21 (1H, q, *J* = 6.9, CHOTBS), 3.19 (1H, qd, *J* = 7.2, *J* = 3.8, COC<u>H</u>$CH_3$CHOH), 1.70 (3H, ddd, *J* = 6.5, *J* = 1.7, *J* = 0.9, HC=CHC<u>H</u>$_3$), 1.30 (3H, d, *J* = 6.9, C<u>H</u>$_3$CHOTBS), 1.11 (3H, d, *J* = 7.2, COCHC<u>H</u>$_3$CHOH), 0.90 (9H, s, SiC$(CH_3)_3$), 0.07 (6H, s, Si$(CH_3)_2$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 217.7, 130.7, 127.7, 74.6, 72.2, 45.2, 25.7, 21.0, 18.0, 17.7, 11.1, –4.6, –5.0. **HRMS (+FAB)**: *m/z* $[M+H]^+$ found 287.2050, $C_{15}H_{31}O_3Si$ requires 287.2042.

**(2*S*,4*R*,5*S*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4,7-dimethyl-3-octanone (5c)**

Colourless oil. $\mathbf{R_f}$ (hexanes/EtOAc 9:1) = 0.3. $\mathbf{[\alpha]_D}$ = +2.7 (*c* = 2.1, $CHCl_3$). **IR** (film): υ 3500, 1720 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.21 (1H, q, *J* = 6.8, CHOTBS), 3.94 (1H, ddd, *J* = 9.3, *J* = 4.1, *J* = 2.9, C<u>H</u>OH), 3.08 (1H, qd, *J* = 7.2, *J* = 2.9, COC<u>H</u>$CH_3$CHOH), 1.85–1.70 (1H, m, C<u>H</u>$(CH_3)_2$, 1.55–1.42 (1H, m, C<u>H</u>$_x$H$_y$CH$(CH_3)_2$), 1.34 (3H, d, *J* = 6.8, C<u>H</u>$_3$CHOTBS), 1.14 (3H, d, *J* = 7.2, COCHC<u>H</u>$_3$CHOH), 1.15–1.00 (CH$_x$<u>H</u>$_y$CH$(CH_3)_2$), 0.92 (9H, s, SiC$(CH_3)_3$), 0.92 (3H, d, *J* = 6.8,

$C\underline{H}_3CHCH_3$), 0.91 (3H, d, $J$ = 6.5, $CH_3CHC\underline{H}_3$), 0.095 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 219.2, 74.6, 68.8, 44.5, 43.1, 25.7, 24.5, 23.4, 22.0, 21.3, 18.0, 10.1, –4.6, –5.0. **HRMS (+FAB)**: *m/z* $[M+H]^+$ found 303.2362, $C_{16}H_{35}O_3Si$ requires 303.2355.

**(2*S*,4*R*,5*S*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4,6-dimethyl-3-heptanone (5d)**

Colourless oil. **$R_f$** (hexanes/EtOAc 9:1) = 0.2. **$[\alpha]_D$** = +24.7 ($c$ = 0.89, $CHCl_3$). **IR** (film): υ 3530, 1702 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.19 (1H, q, $J$ = 7.0, CHOTBS), 3.42 (1H, dd, $J$ = 8.8, $J$ = 2.4, C$\underline{H}$OH), 3.32 (1H, qd, $J$ = 7.15, $J$ = 2.4, COC$\underline{H}CH_3$CHOH), 1.72–1.62 (1H, m, C$\underline{H}(CH_3)_2$), 1.32 (3H, d, $J$ = 7.0, $C\underline{H}_3$CHOTBS), 1.11 (3H, d, $J$ = 7.15, $COCHC\underline{H}_3CHOH$), 1.00 (3H, d, $J$ = 6.6, $C\underline{H}_3CHCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 0.82 (3H, d, $J$ = 6.8, $CH_3CHC\underline{H}_3$), 0.07 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 219.7, 76.0, 74.6, 41.3, 30.4, 25.7, 21.4, 19.4, 18.8, 18.0, 9.4, –4.7, –5.0. **HRMS (+FAB)**: *m/z* $[M+H]^+$ found 289.2207, $C_{15}H_{33}O_3Si$ requires 289.2199.

**(1*S*,2*R*,4*S*)-4-*tert*-Butyldiphenylsilyloxy-1-hydroxy-2-methyl-1-phenyl-3-pentanone (8a)**

Colourless oil. **$R_f$** (hexanes/EtOAc 95:5) = 0.2. **$[\alpha]_D$** = –42.6 ($c$ = 2.8, $CHCl_3$). **IR** (film): υ 3500, 1721 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.70–7.60 (4H, m, ArH), 7.50–7.20 (11H, m, ArH), 4.74 (1H, d, $J$ = 8.1, C$\underline{H}$OH), 4.25 (1H, q, $J$ = 6.9, CHOTBDPS), 3.35 (1H, dq, $J$ = 8.1, $J$ = 7.3, COC$\underline{H}CH_3$CHOH), 1.19 (3H, d, $J$ = 6.9, $C\underline{H}_3$CHOTBDPS), 1.11 (9H, s, $SiC(CH_3)_3$), 0.77 (3H, d, $J$ = 7.3, $COCHC\underline{H}_3CHOH$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 216.6, 142.2, 135.9, 135.8, 133.5, 132.8, 129.9, 129.8, 128.4, 127.8, 127.7, 127.6, 126.6, 76.4, 75.2, 48.4, 26.9, 20.4, 19.2, 14.6. **HRMS (+FAB)**: *m/z* $[M+H]^+$ found 447.2353, $C_{28}H_{35}O_3Si$ requires 447.2355.

**(2*S*,4*R*,5*R*,6*E*)-2-*tert*-Butyldiphenylsilyloxy-5-hydroxy-4-methyl-6-octen-3-one (8b)**

Colourless oil. **$R_f$** (hexanes/EtOAc 95:5) = 0.1. **$[\alpha]_D$** = –8.4 ($c$ = 1.1, $CHCl_3$). **IR** (film): υ 3500, 1719 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.70–7.60 (4H, m, ArH), 7.45–7.35 (6H, m, ArH), 5.65 (1H, dqd, $J$ = 15.3, $J$ = 6.5, $J$ = 0.9, HC=C$\underline{H}CH_3$), 5.36 (1H, ddq, $J$ = 15.3, $J$ = 7.5, $J$ = 1.7, $\underline{H}C$=$CHCH_3$), 4.26 (1H, q, $J$ = 6.9, CHOTBDPS), 4.15–4.05 (1H, m, C$\underline{H}$OH), 3.04 (1H, quintet, $J$ = 7.2, COC$\underline{H}CH_3$CHOH), 1.68 (1H, ddd, $J$ = 6.5, $J$ = 1.7, $J$ = 0.6, HC=CHC$\underline{H}_3$), 1.24 (3H, d, $J$ = 6.9, $C\underline{H}_3$CHOTBDPS), 1.11 (9H, s, $SiC(CH_3)_3$), 0.89 (3H, d, $J$ = 7.2, $COCHC\underline{H}_3CHOH$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 216.6, 135.9, 135.8, 133.6, 132.8, 131.6, 129.9, 129.8, 128.6, 127.7, 127.6, 75.0,

74.9, 46.6, 26.9, 20.5, 19.2, 17.7, 14.3. **HRMS (+FAB)**: *m/z* $[M–OH]^+$ found 393.2253, $C_{25}H_{33}O_2Si$ requires 393.2250.

**(2*S*,4*R*,5*R*)-2-*tert*-Butyldiphenylsilyloxy-5-hydroxy-4,7-dimethyl-3-octanone (8c)**

Colourless oil. $\mathbf{R_f}$ (hexanes/EtOAc 9:1) 0.5. **IR** (film): υ 3460, 1720 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.70–7.60 (4H, m, ArH), 7.50–7.30 (6H, m, ArH), 4.25 (1H, q, *J* = 6.9, CHOTBDPS), 3.72–3.64 (1H, m, C<u>H</u>OH), 2.96 (1H, qd, *J* = 7.2, *J* = 6.2, COC<u>H</u>CH$_3$CHOH), 1.84–1.78 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.32–1.28 (1H, m, C<u>H</u>$_x$H$_y$CH(CH$_3$)$_2$), 1.26 (3H, d, *J* = 6.9, C<u>H</u>$_3$CHOTBDPS), 1.11 (9H, s, SiC(CH$_3$)$_3$), 1.10–1.05 (1H, m, CH$_x$<u>H</u>$_y$CH(CH$_3$)$_2$), 0.96 (3H, d, *J* = 7.2, COCHC<u>H</u>$_3$CHOH), 0.90 (3H, d, *J* = 6.7, C<u>H</u>$_3$CHCH$_3$), 0.86 (3H, d, *J* = 6.5, CH$_3$CHC<u>H</u>$_3$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 217.7, 135.9, 135.8, 133.6, 132.8, 130.0, 129.9, 127.8, 127.7, 74.9, 71.9, 46.9, 44.0, 26.9, 24.4, 23.8, 21.5, 20.8, 19.2, 14.4. **HRMS (+FAB)**: *m/z* $[M+H]^+$ found 427.2654, $C_{26}H_{39}O_3Si$ requires 427.2668.

**(2*S*,4*R*,5*R*)-2-*tert*-Butyldiphenylsilyloxy-5-hydroxy-4,6-dimethyl-3-heptanone (8d)**

Colourless oil. $\mathbf{R_f}$ (hexanes/EtOAc 95:5) 0.10. $\mathbf{[\alpha]_D}$ = +3.8 (*c* = 2.1, $CHCl_3$). **IR** (film): υ 3525, 1719 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.70–7.60 (4H, m, ArH), 7.45–7.35 (6H, m, ArH), 4.26 (1H, q, *J* = 6.9, CHOTBDPS), 3.50–3.45 (1H, m, C<u>H</u>OH), 3.22 (1H, quintet, *J* = 7.3, COC<u>H</u>CH$_3$CHOH), 1.72 (1H, heptd, *J* = 6.8, *J* = 4.3, C<u>H</u>(CH$_3$)$_2$), 1.24 (3H, d, *J* = 6.9, C<u>H</u>$_3$CHOTBDPS), 1.11 (9H, s, SiC(CH$_3$)$_3$), 0.96 (3H, d, *J* = 7.3, COCHC<u>H</u>$_3$CHOH), 0.92 (3H, d, *J* = 6.8, C<u>H</u>$_3$CHCH$_3$), 0.85 (3H, d, *J* = 6.8, CH$_3$CHC<u>H</u>$_3$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 217.4, 135.9, 135.8, 133.6, 132.6, 129.9, 129.8, 127.7, 127.6, 77.7, 75.1, 43.9, 29.9, 26.9, 20.8, 20.1, 19.2, 15.5, 14.3. **HRMS (+FAB)**: *m/z* $[M+H]^+$ found 413.2521, $C_{25}H_{37}O_3Si$ requires 413.2512.

**Stereochemical proof of aldol diastereomer 5a.**

Aqueous 48% HF (0.11 mL, 3.4 mmol) was added dropwise to a solution of **5a** (229 mg, 0.7 mmol) in $CH_3CN$ (6 mL) and stirred at room temperature for 45 min. The mixture was partitioned between $CH_2Cl_2$ (200 mL) and 1 M NaOH (50 mL); the organic layer was dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification of the resulting oil by column chromatography (hexanes/EtOAc 70:30) afforded (97 mg, 66%) pure (1*R*,2*R*,4*S*)-1,4-dihydroxy-2-methyl-1-phenyl-3-pentanone, **10**.

Colourless oil. **$R_f$** (hexanes/EtOAc 70:30) 0.10. **$^1$H NMR** (200 MHz, $CDCl_3$) δ 7.35–7.20 (5H, m, ArH), 5.02 (1H, d, *J* = 5.4, PhC<u>H</u>OH), 4.29 (1H, q, *J* = 7.2, $CH_3$C<u>H</u>OHCO), 3.05 (1H, dq, *J* = 7.2, *J* = 5.4, COC<u>H</u>$CH_3$), 1.15 (3H, d, *J* = 7.2, $CH_3$), 1.04 (3H, d, *J* = 7.2, $CH_3$). **$^{13}$C NMR** (50.3 MHz, $CDCl_3$) δ 216.1, 141.7, 128.3, 127.7, 126.1, 73.3, 71.5, 48.6, 18.9, 12.4.

A solution of **10** (97 mg, 0.47 mmol) and $NaIO_4$ (994 mg, 4.65 mmol) in MeOH/$H_2O$ 2:1 (2.6 mL) was stirred for 2.5 h at room temperature. The mixture was partitioned between 0.5 M HCl (20 mL) and $Et_2O$ (3 × 30 mL); the combined ethereal extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was diluted with $CH_2Cl_2$ (20 mL) and extracted with 0.1 M NaOH (2 × 20 mL); the aq. extracts were combined, cooled to 0 °C and 37% HCl was added carefully until pH ~ 1. The acidic mixture was extracted with $CH_2Cl_2$ (4 × 30 mL); the organic portions were combined, dried ($Na_2SO_4$) and concentrated *in vacuo*. Spectroscopic and physical data of the resulting product (50 mg, 60%) showed that it was (2*R*,3*R*)-3-hydroxy-2-methyl-3-phenylpropanoic acid, **11**.

White solid. **$[\alpha]_D$** = +32.4 (*c* = 1.0, $CHCl_3$) (lit.[1] **$[\alpha]_D$** = +31.03 (*c* = 1.07, $CHCl_3$); lit.[2] **$[\alpha]_D$** = +33.6 (*c* = 0.7, $CHCl_3$)). **IR** (KBr): υ 3477, 3200–2800 (broad), 1696 $cm^{-1}$. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.25 (5H, m, ArH), 5.16 (1H, d, *J* = 4.0, C<u>H</u>OH), 2.84 (1H, dq, *J* = 7.2, *J* = 4.0, COCH), 1.14 (3H, d, *J* = 7.2, $CH_3$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 180.7, 141.0, 128.3, 127.6, 125.9, 73.4, 46.1, 10.2.

**Stereochemical proof of aldol diastereomer 8d.**

Aqueous 48% HF (0.27 mL, 7.5 mmol) was added dropwise to a solution of **8d** (308 mg, 0.75 mmol) in $CH_3CN$ (3 mL) and stirred overnight at room temperature. The mixture was partitioned between $CH_2Cl_2$ (100 mL) and sat. $NaHCO_3$ (2 × 50 mL); the organic layer was dried ($Na_2SO_4$) and concentrated *in vacuo*. Purification of the resulting oil by column chromatography (hexanes/EtOAc 9:1) afforded (91 mg, 70%) pure (2*S*,4*R*,5*R*)-2,5-dihydroxy-4,6-dimethyl-3-heptanone, **12**.

Colourless oil. **$R_f$** (hexanes/EtOAc 9:1) 0.10. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 4.32 (1H, q, *J* = 7.0, $CH_3$C<u>H</u>OHCO), 3.61 (1H, dd, *J* = 8.4, *J* = 3.2, COCHC$H_3$C<u>H</u>OH), 3.11 (1H, dq, *J* = 8.4, *J* = 7.0, COC<u>H</u>C$H_3$CHOH), 1.81 (1H, heptd, *J* = 6.8, *J* = 3.2, C<u>H</u>$(CH_3)_2$), 1.36 (3H, d, *J* = 7.0, C<u>H</u>$_3$CHOHCO), 1.06 (3H, d, *J* = 7.0, COCHC<u>H</u>$_3$CHOH), 0.98 (3H, d, *J* = 6.8, C<u>H</u>$_3$C$H_3$), 0.92

[1] Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

[2] Ghosh, A. K.; Cho, H.; Onishi, M. *Tetrahedron: Asymmetry* **1997**, *8*, 821.

(3H, d, $J$ = 6.8, $CH_3CHC\underline{H}_3$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 217.7, 77.9, 72.3, 43.4, 29.6, 19.9, 19.5, 14.6, 14.3.

A solution of **12** (91 mg, 0.52 mmol) and $NaIO_4$ (1.12 g, 5 mmol) in MeOH/$H_2O$ 2:1 (6 mL) was submitted to the same experimental procedure previously reported. Spectroscopic and physical data of the resulting product (28 mg, 37%) showed that it was (2*R*,3*R*)-3-hydroxy-2,4-dimethylpentanoic acid, **13**.

Colourless oil. **[α]$_D$** = –12.6 (*c* = 1.4, $CHCl_3$) (lit.[3] **[α]$_D$** = –17.6 (*c* = 0.49, $CHCl_3$); lit.[4] **[α]$_D$** = –14.3 (*c* = 1.0, $CHCl_3$)). **IR** (film): υ 3450, 3300–2800 (broad), 1690 cm$^{-1}$. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 3.45–3.40 (1H, m, C$\underline{H}$OH), 2.69 (1H, quintet, $J$ = 7.1, COC$\underline{H}CH_3$), 1.85–1.70 (1H, m, C$\underline{H}(CH_3)_2$), 1.25 (3H, d, $J$ = 7.1, $CH_3$), 0.99 (3H, d, $J$ = 6.9, $CH_3$), 0.94 (3H, d, $J$ = 6.7, $CH_3$). **$^{13}$C NMR** (75.4 MHz, $CDCl_3$) δ 181.1, 76.6, 42.6, 30.8, 19.7, 16.1, 14.6.

[3] Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T.-H. *J. Org. Chem.* **1996**, *61*, 2038.

[4] Van Draanen, N. A; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499.