Chiral Dihydroxyacetone Equivalents in Synthesis: An Expedient Diastereo- and Enantioselective Synthesis of Differentially Protected Ketopolyols

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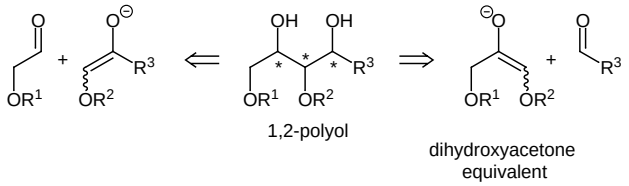
Abstract: A highly diastereo- and enantioselective entry to higher order ketopolyols, employing boron-mediated aldol reactions of a chiral dihydroxyacetone equivalent, is reported. The differentially protected products should prove as useful building blocks for polyhydroxylated natural product synthesis.

Key words: chiral dihydroxyacetone equivalent, α-substituted ketones, aldol reactions, polyols, asymmetric synthesis



Scheme 1

An efficient approach to asymmetric 1,2-diol synthesis involves the establishment of the required relative and absolute stereochemistry with concommitant C–C bond formation. The combination of an aldehyde and a (formal) carbon-centred nucleophile in which either of the reacting partners contains α-hydroxy substitution fulfills these criterea. An interesting possibility for 1,2-*polyol* synthesis is revealed when *both* the aldehyde and carbon-centred nucleophile are α-hydroxylated (Scheme 1). In this context, the asymmetric aldol reaction involving an α-hydroxycarbonyl compound has been shown as a reliable method, with both *syn*- and *anti*-diastereoisomers accessible.[1] Most of the research has focussed on aldol-type reactions of suitable glycolic acid derivatives.[2] The aldol reaction of 2-(trimethylsilyloxy)furan and α-oxygenated aldehydes has also been utilised with success.[3] An alternative route is presented when the attacking enolate is at the ketone oxidation level, thus indicating a directed reduction as the final step. This immediately poses the issue of regioselective enolisation.[4] Paterson has employed chiral propionate- and lactate-derived protected α-hydroxy ketones in highly diastereoselective boron-mediated aldol reactions.[1f,5] Recently, Sasaki et al. made elegant use of a lactate-derived chiral α-hydroxy ketone in natural product synthesis.[6] Alternatively, in new developments, the direct regioselective enolisation of unprotected α-hydroxy ketones has been demonstrated with biological catalysts[7] as well as small organic promoters[8] and bimetallic complexes.[9]

The problem is simplified when the enolate component contains both α-hydroxy centres thus requiring a dihydroxyacetone (DHA) equivalent (Scheme 1). This strategy may be considered biomimetic as nature performs asymmetric aldol reactions on dihydroxyacetone phosphate (DHAP) in carbohydrate biosynthesis. It is therefore not unsurprising that one of the major areas of research on DHA and its derivatives has been in the area of enzyme-catalysed aldol reactions.[1b,10] In marked contrast, chemical equivalents of dihydroxyacetone have only been employed in aldol reactions relatively recently. Diastereoselectivity has been observed in boron-mediated aldol reactions of 2,2-dimethyl-1,3-dioxan-5-one[11] and in Mukaiyama aldol reactions of the *Z*-silyl enol ether of 1,3-di-*O*-benzyloxyacetone[12] and the corresponding cyclohexylidene derivative.[12b] The enolisation of a variety of protected acyclic DHA derivatives with the usually *E*-selective dicyclohexylboron chloride/triethylamine system has been reported to give 1,2-*syn* selectivity.[13] In the same work, regioselective enolisation of an unsymmetrical DHA derivative was reported in which enolisation towards an *O*-acyl group but away from a bulky *O*-silyl group occurred.

The development of only a few chiral DHAP derivatives has been reported. In 1988 Hirama showed that the lithium enolate of an α-substituted dioxanone (synthesised in five steps from D-glucose) could participate in a 1,2-*anti* selective aldol reaction.[14] A conceptually similar bis-acetal erythrulose derivative was employed by Carda and Marco et al. in boron-mediated aldol reactions.[15] By altering the nature of the protecting groups, 1,2-*syn* or 1,2-*anti* diastereoselectivity could be achieved.

In 1995, a potentially more general approach was pioneered by Majewski in which a simple prochiral dioxanone was deprotonated by a chiral lithium amide base and the resulting anion trapped with aldehydes to give 1,2-*anti* products.[16] More recent work has shown that the combination of prochiral ketone, chiral base and chiral aldehyde is essential for high enantioselectivity.[11]

In 1993 our group reported a solution to the problem of introducing chirality to a simple DHA system by conversion of 2,2-dimethyl-1,3-dioxan-5-one to the corresponding

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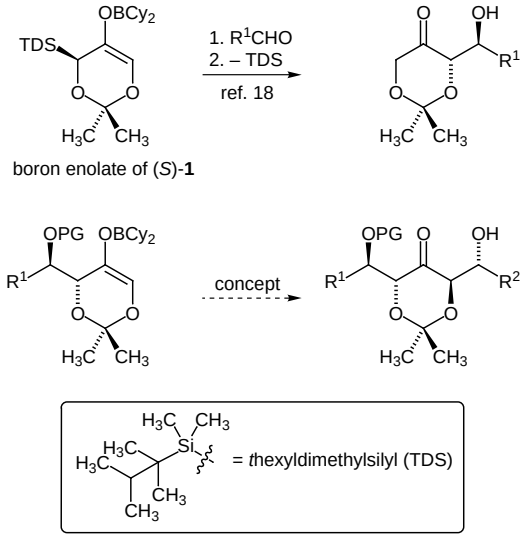
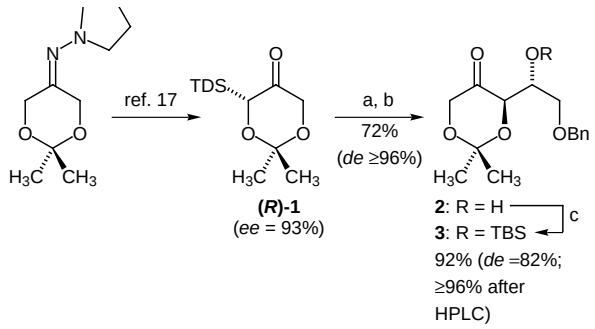
SAMP or RAMP hydrazone.[17] The azaenolate, generated by deprotonation with *t*-BuLi at low temperature, reacted with aldehydes to give, after cleavage of the auxiliary, the 1,2-*anti* diastereomers with de's up to 79% and ee's up to 82%. Interestingly, the reaction with benzyl glyoxylate returned the 1,2-*syn* diastereoisomer. However, the boron enolate of chiral DHA equivalent (*S*)-**1** (readily available from the corresponding SAMP hydrazone) reacted smoothly with a variety of aldehydes to give, after cleavage of the α-silyl auxiliary, protected keto triols as single diastereoisomers in excellent enantiomeric purity (Scheme 2).[18] We realised that suitable protection of the free hydroxyl would offer the possibility of a *second* aldol reaction whose stereoselectivity should be controlled in the same way and thus offer access to higher order polyol sytems.[19]



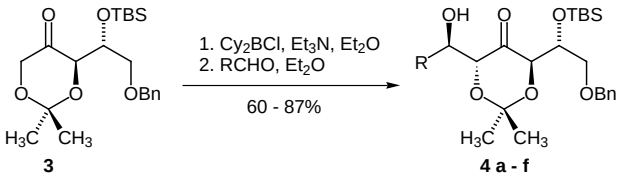
Scheme 2

In this paper we wish to report the extension of this methodology in a practical approach to differentially protected ketopolyols. The four new oxygenated stereogenic centres are all induced from the single stereogenic centre in the simple, RAMP hydrazone derived, α-silyldioxanone (*R*)-**1**. To selectively manipulate oxygen functionality, an orthogonally cleavable protecting group was required for the β-hydroxyl. In this respect a silyl ether was attractive. Benzyloxyacetaldehyde was chosen as the first aldehyde, offering the advantage of a benzyl ether cleavable by hydrogenolysis. α-Silyldioxanone (*R*)-**1** was prepared in two steps from the corresponding dioxanone RAMP hydrazone in analogy to our previous work (Scheme 3).[18] In this case the ee, as determined by GC (chiral stationary phase), was 93%. Hydroxy ketone **2** was also prepared in analogy to the previous work. Furthermore, we have found that the use of dimethylethylamine as amine base is no longer necessary as triethylamine performs equally well. As expected the aldol product was isolated in high yield (86%) and diastereoselectivity (≥96% de). Subsequent desilylation with triethylamine HF complex was also uneventful and once again no detectable epimerisation was observed. Silylation of hydroxy ketone **2** with TBSOTf and 2,6-lutidine as the base gave the required aldol precusor **3** in excellent yield. Slight epimerisation of the α-stereogenic centre (de as low as 82%) was observed in some reactions, the exact origin of which is not clear at present. No silyl enol ether formation could be detected. Diastereomerically pure **3** (≥96% de), however, was obtainable by preparative HPLC.



Scheme 3 *Reagents and conditions*: (a) Cy_2BCl, Et_3N, Et_2O, –78 to 0 °C, then $BnOCH_2CHO$, Et_2O, –78 to –24 °C, 86%; (b) $Et_3N{\cdot}3HF$, THF, –20 °C, 84%; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 92%

We next investigated the reactivity of **3** in the boron-mediated aldol reaction with a range of aldehydes (Scheme 4). Thus, ketone **3** was reacted with a mixture of Cy_2BCl (1.5 equiv) and Et_3N (1.7 equiv) in diethyl ether at low temperature (–78 °C) before warming to 0 °C. The resulting boron enolate was recooled to –78 °C before a solution of the corresponding aldehyde (1.3 – 2.5 equiv) in diethyl ether was added and the reaction was stirred at –78 °C for 1 hour before warming to –24 °C. Subsequent oxidative workup (30% aq H_2O_2, MeOH/pH 7 buffer) afforded the crude aldol products that were purified by chromatography. In this way, hydroxy ketones **4a**–**f** were isolated in good yields (60–87%) and with excellent diastereoselectivities (≥96% de) (Scheme 4, Table). It is important to note that employment of an oxidative workup is essential to isolate pure products. Crude **4d** for example, could not be separated from the lactol product between PhCHO and Cy_2BOH. The lower yields of the reactions in some cases may reflect an increased sensitivity towards this oxidative workup.[20]



Scheme 4

In summary the bis-aldol strategy outlined above has allowed rapid access to differentially protected higher order ketopolyols. The presence of three orthogonal protecting groups, the possibility of a subsequent directed reduction

Table Cy_2BCl-Mediated Diastereoselective Aldol Reactions of Ketone **3** to Form the Protected Ketopolyols **4** (93% ee)

4	R	Yield[a] (%)	$[\alpha]_D$[b]	de[c] (%)
a	Pr	64	+65.8	≥96
b	*i*Pr	66	+67.7	≥96
c	CH_2=C(Me)	83	+60.7	≥96
d	Ph	87	+53.5	≥96
e	$(CH_2)_2$OTBDPS	84	+42.1	≥96
f	CH_2OBn	60	+66.7	≥96

[a] Yields after chromatography.
[b] Measured at 26 ± 1.0 °C, *c* = 1.0, $CHCl_3$.
[c] Determined by ^{1}H and ^{13}C NMR spectroscopy.

and the access to both enantiomeric forms makes this approach attractive and flexible for polyhydroxylated natural product synthesis with which we are now engaged.

Anhyd CH_2Cl_2 was distilled from CaH_2, MeOH was distilled from Mg, anhyd Et_2O and THF were distilled from Na/Pb alloy (benzophenone indicator). Anhyd Et_3N was stored over and distilled from CaH_2. Anhyd 2,6-lutidine was distilled from CaH_2 and stored over activated 4Å molecular sieves. Cy_2BCl was prepared using commercial (Aldrich) $H_2BCl{\cdot}SMe_2$ complex.[1f] (*R*,*R*)-4-(2-Benzyloxy-1-hydroxyethyl)-2,2-dimethyl[1,3]dioxan-5-one (**2**) (93% ee, $[\alpha]_D$ +96.6 (*c* = 0.73, $CHCl_3$) {Lit.[18] [for (*S*,*S*)-enantiomer] –107 (*c* = 1.0, $CHCl_3$)} was prepared in analogy to our published procedure. 3-(*tert*-Butyldiphenylsilanyloxy)propionaldehyde was prepared in two steps (silylation, Dess–Martin oxidation) from propane-1,3-diol.[21] Benzyloxyacetaldehyde was prepared in two steps (benzylation, oxidative cleavage) from (*Z*)-but-2-ene-1,4-diol.[22] All other reagents were obtained commercially and used without further purification.

Reactions were carried out at r.t. under argon in predried glassware using anhyd solvents unless otherwise stated. Distilled H_2O was used. All aqueous solutions were saturated unless otherwise stated. Phosphate buffer (pH 7) was a solution of KH_2PO_4 (34.0 g) and NaOH (5.82 g) in H_2O (500 mL). Distilled solvents were used for for chromatography and reaction workup. Column chromatography was carried out under pressure using Merck silica gel (400–630 mesh). Analytical and preparative TLC was performed using precoated, glass backed plates (Merck silica gel 60 F 254) and visualised by ultra violet radiation (254 nm), acidic ammonium molybdate(IV) or alkaline $KMnO_4$.

Optical rotations were measured with a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1760 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Gemini 300 MHz, Varian Inova 400 MHz and Unity 500 MHz spectrometers using TMS as reference. *J* values are given in Hz. Signals were assigned by means of 2D spectra (COSY, HETCOR) and APT. Mass spectra were obtained on a Finnigan SSQ7000 spectrometer (CI 100 eV; EI 70 eV) and high resolution mass spectra on a Finnigan MAT 95. Microanalyses were determined on a Heraeus CHN-O-RAPID or an Elementar Vario EL.

(*R*,*R*)-4-[2-Benzyloxy-1-(*tert*-butyldimethylsilanyloxy)ethyl]-2,2-dimethyl[1,3]dioxan-5-one (3)

To a stirred solution of the hydroxy ketone **2**[18] (0.87 g, 3.10 mmol, 1.0 equiv) in CH_2Cl_2 (3.8 mL) at –78 °C was added sequentially, distilled 2,6-lutidine (1.44 mL, 12.4 mmol, 4.0 equiv) and TBSOTf (2.18 mL, 9.31 mmol, 3.0 equiv) dropwise via syringe. The stirring was continued for a further 75 min before the reaction was quenched at –78 °C with aq $NaHCO_3$ solution (10 mL) and warmed to r.t. The mixture was poured into aq $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (50 mL). The aqueous portion was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to give the crude product as a colourless syrup. Purification by flash chromatography on silica gel (eluent: 97:3 → 9:1 pentane–Et_2O) gave the title compound **3** (1.13 g, 92%, 82% de) as a colourless syrup; $[\alpha]_D^{22}$ +76.8 (*c* = 1.0, $CHCl_3$).

IR (film): 3031, 2987, 2953, 2930, 2886, 2857, 1751, 1497, 1472, 1462, 1375, 1326. 1303, 1252, 1225, 1160, 1100, 1029, 1006 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.87 [s, 9 H, $SiC(CH_3)_3$], 1.43 (s, 3 H, CH_3 acetal), 1.44 (s, 3 H, CH_3 acetal), 3.51 (dd, *J* = 9.7, 6.2 Hz, 1 H, C*H*$_a$H$_b$OBn), 3.72 (dd, *J* = 9.6, 7.7 Hz, 1 H, CH$_a$*H*$_b$OBn), 3.86 (d, *J* = 15.9 Hz, 1 H, H-6a), 4.18 (dd, *J* = 15.9, 1.4 Hz, 1 H, H-6b), 4.32–4.36 (m, 2 H, H-4, C*H*OTBS), 4.15–4.54 (q_{AB}, 2 H, C*H*$_2$Ph), 7.25–7.35 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, –4.3 [$Si(CH_3)_2$], 18.5 [Si*C*$(CH_3)_3$], 23.4, 25.2 (CH_3 acetal), 26.1 [$SiC(CH_3)_3$], 67.4 (*C*H_2OBn), 70.8 (C-6), 71.7 (C-4/*C*HOTBS), 73.6 (*C*H_2Ph), 77.7 (C-4/*C*HOTBS), 100.5 (acetal C), 127.8, 128.5 (Ar-C), 138.3 (Ar-C, *ipso*), 206.9 (C=O).

MS (CI): *m*/*z* (%) = 396.3 (30, MH^+ + 1), 395.3 (100, MH^+), 377.3 (13), 338.3 (16), 337.3 (67), 319.3 (10), 287.2 (16), 279.2 (21), 265.2 (11), 205.2 (16), 187.1 (26), 161.2 (10), 155.1 (12), 145.1 (30), 133.2 (10), 91.3 (32).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{19}O_4Si$ ($M^+ - C_7H_{15}O$), 279.1053; found, 279.1046.

Anal. Calcd for $C_{21}H_{34}O_5Si$ (394.6): C, 63.92; H, 8.69. Found C, 63.61; H, 9.21.

Boron-Mediated Aldol Reactions of Ketone 3; General Procedure

To a stirred solution of Cy_2BCl (1.5 equiv) in Et_2O (20 mL/mmol ketone), at –78 °C, was added Et_3N (1.7 equiv) via syringe followed, 10 min later, by a solution of the ketone **3** (1 equiv) in Et_2O (2 mL/mmol), via syringe. Stirring was continued for a further 30 min at –78 °C, before the mixture was warmed to 0 °C for 1 h. The resulting suspension was recooled to –78 °C before a solution of the freshly purified aldehyde (1.3–2.5 equiv) in Et_2O (3 mL/mmol ketone) was added dropwise via syringe. The stirring was continued for 1 h at –78 °C before the flask was sealed and placed in a freezer (–24 °C) for 14–18 h. The mixture was quenched with phosphate buffer (pH 7, 20 mL/mmol ketone) and extracted with Et_2O (2 volumes). The combined organic extracts were concentrated in vacuo, taken up in phosphate buffer (pH 7, 6 mL/mmol ketone) and MeOH (6 mL/mmol ketone) and cooled to 0 °C before aq H_2O_2 (30%, 3 mL/mmol ketone) was added dropwise. The mixture was warmed to r.t. over 1–2 h, poured into phosphate buffer (pH 7, 20 mL/mmol ketone) and extracted with CH_2Cl_2 (4 volumes). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to give the crude product as a colourless or yellow syrup. Purification by flash chromatography on silica gel (gradients of pentane–Et_2O) gave the hydroxy ketones as a colourless or pale yellow syrup.

(*R*,*R*,*R*,*R*)-4-[2-Benzyloxy-1-(*tert*-butyldimethylsilanyloxy)ethyl]-6-(1-hydroxybutyl)-2,2-dimethyl[1,3]dioxan-5-one (4a)

The boron enolate of ketone **3** (0.25 g, 0.63 mmol) was generated and reacted with freshly distilled *n*-butanal (0.11 mL, 1.27 mmol) according to the general procedure. Oxidative workup and subsequent flash chromatography on silica gel (eluent: 9:1 → 7:1 pen-

tane–Et_2O) gave the title compound **4a** (0.189 g, 64%) as a colourless syrup; $[\alpha]_D^{26}$ +65.8 (*c* = 1.0, $CHCl_3$).

IR (film): 3554, 3031, 2987, 2957, 2931, 2859, 1738, 1463, 1409, 1377, 1310, 1254, 1222, 1172, 1104, 1029, 1006 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.86 [s, 9 H, $SiC(CH_3)_3$], 0.92 (t, *J* = 7.0 Hz, 3 H, $CH_3CH_2CH_2$), 1.30–1.60 (m, 4 H, $CH_3CH_2CH_2$), 1.39 (s, 3 H, CH_3 acetal), 1.43 (s, 3 H, CH_3 acetal), 2.92 (d, *J* = 3.8 Hz, 1 H, CHO*H*), 3.48 (dd, *J* = 9.3, 5.9 Hz, 1 H, CH_aH_bOBn), 3.70 (dd, *J* = 9.3, 8.2 Hz, 1 H, CH_aH_bOBn), 3.76–3.82 (m, 1 H, C*H*OH), 3.94 (dd, *J* = 7.5, 1.1 Hz, 1 H, H-6), 4.27 (dd, *J* = 1.9, 1.1 Hz, 1 H, H-4), 4.33 (ddd, *J* = 8.0, 6.0, 2.0 Hz, 1 H, C*H*OTBS), 4.45 (d, *J* = 11.8 Hz, 1 H, $PhCH_aH_b$), 4.51 (d, *J* = 11.8 Hz, 1 H, $PhCH_aH_b$), 7.26–7.36 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.9, –4.7 [$Si(CH_3)_2$], 14.0 ($CH_3CH_2CH_2$), 18.1 [$SiC(CH_3)_3$], 18.2 ($CH_3CH_2CH_2$), 23.6, 24.2 (CH_3 acetal), 25.7 [$SiC(CH_3)_3$], 34.3 ($CH_3CH_2CH_2$), 69.8 (CHOH), 70.0 (CH_2OBn), 71.3 (CHOTBS), 73.3 ($PhCH_2$), 74.6 (C-6), 76.8 (C-4), 101.0 (acetal C), 127.4, 127.5, 127.6, 128.2 (Ar-C), 137.7 (Ar-C, *ipso*), 209.9 (C=O).

MS (CI): *m*/*z* (%) = 468.3 (34, MH^+ + 1), 467.3 (100, MH^+), 450.3 (20), 449.3 (63), 410.3 (23), 409.2 (86), 396.2 (15), 395.2 (51, MH^+ – *n*-PrCHO), 391.3 (28), 377.2 (13), 337.2 (25), 133.1 (19).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{33}O_6Si$ ($M^+ - C_4H_9$), 409.2046; found, 409.2047; *m*/*z* calcd for $C_{21}H_{31}O_5Si$ ($M^+ - C_4H_{11}O$), 391.1941; found, 391.1940.

Anal. Calcd for $C_{25}H_{42}O_6Si$ (466.7): C, 64.34; H, 9.07. Found C, 64.23; H, 9.71.

(*R*,*R*,*R*,*R*)-4-[2-Benzyloxy-1-(*tert*-butyldimethylsilanyloxy)ethyl]-6-(1-hydroxy-2-methylpropyl)-2,2-dimethyl[1,3]dioxan-5-one (4b)

The boron enolate of ketone **3** (0.294 g, 0.74 mmol) was generated and reacted with freshly distilled 2-methylpropionaldehyde (0.10 mL, 1.12 mmol) according to the general procedure. Oxidative workup and subsequent flash chromatography on silica gel (eluent: 98:2 → 9:1 pentane–Et_2O) gave the title compound **4b** (0.231 g, 66%) as a colourless syrup; $[\alpha]_D^{26}$ +67.7 (*c* = 1.0, $CHCl_3$).

IR ($CHCl_3$): 3556, 3031, 2958, 2931, 2880, 2858, 1736, 1472, 1464, 1456, 1404, 1382, 1375, 1343, 1321, 1252, 1220, 1173, 1108, 1044, 1029, 1006 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.87–0.89 [m, 12 H, $SiC(CH_3)_3$, $CHCH_3$], 0.99 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 1.39 (s, 3 H, CH_3 acetal), 1.44 (s, 3 H, CH_3 acetal), 1.95–1.99 [m, 1 H, $CH(CH_3)_2$], 2.96 (d, *J* = 3.0 Hz, 1 H, CHO*H*), 3.48 (dd, *J* = 9.2, 5.9 Hz, 1 H, CH_aH_bOBn), 3.66 (ap dt, *J* = 8.5, 3.0 Hz, 1 H, C*H*OH), 3.71 (dd, *J* = 9.2, 8.1 Hz, 1 H, CH_aH_bOBn), 4.04 (dd, *J* = 8.4, 1.0 Hz, 1 H, H-6), 4.29 (ap t, *J* = 1.8 Hz, 1 H, H-4), 4.34 (ddd, *J* = 8.0, 6.0, 1.9 Hz, 1 H, C*H*OTBS), 4.46 (d, *J* = 11.8 Hz, 1 H, $PhCH_aH_b$), 4.52 (d, *J* = 11.8 Hz, 1 H, $PhCH_aH_b$), 7.26–7.36 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.3 [$Si(CH_3)_2$], 15.4 ($CHCH_3$), 18.5 [$SiC(CH_3)_3$], 19.7 ($CHCH_3$), 24.0, 24.8 (CH_3 acetal), 26.1 [$SiC(CH_3)_3$], 28.7 [$CH(CH_3)_2$], 70.3 (CH_2OBn), 71.8 (CHOTBS), 72.8 (C-6), 73.7 ($PhCH_2$), 73.9 (CHOH), 77.2 (C-4), 101.3 (acetal C), 127.9, 128.0, 128.6 (Ar-C), 138.1 (Ar-C, *ipso*), 211.3 (C=O).

MS (CI): *m*/*z* (%) = 468.4 (30, MH^+ + 1), 467.4 (100, MH^+), 450.4 (15, $MH^+ + 1 - H_2O$), 449.3 (50, $MH^+ - H_2O$), 410.3 (10), 409.3 (34), 395.3 (20, MH^+ – *i*-PrCHO), 391.3 (15), 377.3 (12), 337.3 (16), 205.1 (11).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{27}O_5Si$ ($M^+ - C_7H_{15}O$), 351.1623; found, 351.1628.

Anal. Calcd for $C_{25}H_{42}O_6Si$ (466.7): C, 64.34; H, 9.07. Found C, 64.22; H, 8.82.

(*R*,*R*,*R*,*R*)-4-[2-Benzyloxy-1-(*tert*-butyldimethylsilanyloxy)ethyl]-6-(1-hydroxy-2-methylallyl)-2,2-dimethyl[1,3]dioxan-5-one (4c)

The boron enolate of ketone **3** (0.25 g, 0.63 mmol) was generated and reacted with freshly distilled 2-methylpropenal (0.10 mL, 1.27 mmol) according to the general procedure. Oxidative workup and subsequent flash chromatography on silica gel (eluent: 10:1 pentane–Et_2O) gave the title compound **4c** (0.244 g, 83%) as a colourless syrup which upon storage at –24 °C solidified to an amorphous white solid; $[\alpha]_D^{26}$ +60.7 (*c* = 1.0, $CHCl_3$).

IR (KBr): 3547, 3087, 3065, 3030, 2991, 2956, 2927, 2894, 2857, 1735, 1496, 1472, 1460, 1380, 1326, 1312, 1261, 1224, 1173, 1150, 1108, 1056, 1039, 1006 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.87 [s, 9 H, $SiC(CH_3)_3$], 1.38 (s, 3 H, CH_3 acetal), 1.40 (s, 3 H, CH_3 acetal), 1.73–1.74 (m, 1 H, $CH_3C=CH_2$), 3.20 (d, *J* = 3.0 Hz, 1 H, CHO*H*), 3.49 (dd, *J* = 9.3, 5.8 Hz, 1 H, CH_aH_bOBn), 3.72 (dd, *J* = 9.3, 8.2 Hz, 1 H, CH_aH_bOBn), 4.09 (dd, *J* = 8.4, 1.2 Hz, 1 H, H-6), 4.21 (dd, *J* = 8.2, 2.7 Hz, 1 H, C*H*OH), 4.30 (dd, *J* = 1.9, 1.1 Hz, 1 H, H-4), 4.34 (ddd, *J* = 8.0, 5.9, 2.1 Hz, 1 H, C*H*OTBS), 4.46 (d, *J* = 12.1 Hz, 1 H, $PhCH_aH_b$), 4.52 (d, *J* = 11.8 Hz, 1 H, $PhCH_aH_b$), 4.95–4.96 (m, 1 H, $CH_3C=CH$)), 5.00–5.01 (m, 1 H, $CH_3C=CH$), 7.26–7.36 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.3 [$Si(CH_3)_2$], 18.3 ($CH_3C=CH_2$), 18.5 [$SiC(CH_3)_3$], 23.9, 24.6 (CH_3 acetal), 26.1 [$SiC(CH_3)_3$], 70.3 (CH_2OBn), 71.7 (CHOTBS), 73.4 (C-6), 73.7 ($PhCH_2$), 74.2 (CHOH), 77.2 (C-4), 101.5 (acetal C), 114.8 ($CH_3C=CH_2$)), 127.9, 128.0, 128.6 (Ar-C), 138.0 (Ar-C, *ipso*), 142.9 ($CH_3C=CH_2$), 210.4 (C=O).

MS (CI): *m*/*z* (%) = 466.4 (24, MH^+ + 1), 465.4 (83, MH^+), 448.4 (20, $MH^+ + 1 - H_2O$), 447.4 (66, $MH^+ - H_2O$), 407.4 (15), 396.3 [28, $MH^+ + 1 - CH_2=C(CH_3)CHO$], 395.3 [100, $MH^+ - CH_2=C(CH_3)CHO$], 378.3 (10), 377.3 (40), 357.3 (31), 337.2 (33), 205.2 (12), 161.2 (28), 127.3 (19), 71.3 (39).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{33}O_5Si$ ($M^+ - C_4H_7O$), 393.2097; found, 393.2095.

Anal. Calcd for $C_{25}H_{40}O_6Si$ (464.7): C, 64.62; H, 8.68. Found C, 64.70; H, 8.93.

(*R*,*R*,*R*,*R*)-4-[2-Benzyloxy-1-(*tert*-butyldimethylsilanyloxy)ethyl]-6-(hydroxyphenylmethyl)-2,2-dimethyl[1,3]dioxan-5-one (4d)

The boron enolate of ketone **3** (0.30 g, 0.76 mmol) was generated and reacted with freshly distilled benzaldehyde (0.12 mL, 1.14 mmol) according to the general procedure. Oxidative workup and subsequent flash chromatography on silica gel (eluent: 8:1 → 6:1 pentane–Et_2O) gave the title compound **4d** (0.331 g, 87%) contaminated by a trace amount of benzaldehyde as a pale yellow syrup; $[\alpha]_D^{26}$ +53.5 (*c* = 1.0, $CHCl_3$).

IR (film): 3533, 3064, 3033, 2987, 2952, 2929, 2895, 2857, 1737, 1496, 1472, 1454, 1406, 1383, 1376, 1363, 1324, 1308, 1252, 1224, 1200, 1170, 1103, 1052, 1029, 1006 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.88 [s, 9 H, $SiC(CH_3)_3$], 1.14 (s, 3 H, CH_3 acetal), 1.32 (s, 3 H, CH_3 acetal), 3.49 (dd, *J* = 9.3, 6.2 Hz, 1 H, CH_aH_bOBn), 3.57 (d, *J* = 3.0 Hz, 1 H, CHO*H*), 3.72 (dd, *J* = 9.2, 8.4 Hz, 1 H, CH_aH_bOBn), 4.17 (dd, *J* = 8.2, 1.4 Hz, 1 H, H-6), 4.31 (dd, *J* = 1.8, 1.2 Hz, 1 H, H-4), 4.36 (ddd, *J* = 8.0, 5.9, 2.1 Hz, 1 H, C*H*OTBS), 4.45 (d, *J* = 12.1 Hz, 1 H, $PhCH_aH_b$), 4.52 (d, *J* = 11.8 Hz, 1 H, $PhCH_aH_b$), 4.77 (dd, *J* = 8.2, 2.7 Hz, 1 H, C*H*OH), 7.25–7.38 (m, 10 H, 2 C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.4, –4.3 [$(Si(CH_3)_2$], 18.5 [Si*C*$(CH_3)_3$], 23.8, 24.2 (CH_3 acetal), 26.1 [SiC(*C*$H_3)_3$], 70.3 (*C*H_2OBn), 71.8 (*C*HOTBS), 72.6 (CHOH), 73.7 (Ph*C*H_2), 75.3 (C-6), 77.4 (C-4), 101.6 (acetal C), 127.2, 127.6, 127.9, 128.0, 128.2, 128.4, 128.6 (Ar-C), 138.0, 139.9 (Ar-C, *ipso*), 210.1 (C=O).

HRMS: *m*/*z* calcd for $C_{17}H_{25}O_5Si$ ($M^+ - C_{11}H_{15}O$), 337.1471; found 337.1473.

(*R*,*R*,*R*,*R*)-4-[2-Benzyloxy-1-(*tert*-butyldimethylsilanyloxy)ethyl]-6-[3-(*tert*-butyldiphenylsilanyloxy)-1-hydroxypropyl]-2,2-dimethyl[1,3]dioxan-5-one (4e)

The boron enolate of ketone **3** (0.25 g, 0.63 mmol) was generated and reacted with freshly prepared 3-(*tert*-butyldiphenylsilanyloxy)propionaldehyde (0.26 mL, 0.82 mmol) according to the general procedure. Oxidative workup and subsequent flash chromatography on silica gel (eluent: 9:1 → 7:1 pentane–Et_2O) gave the title compound **4e** (0.376 g, 84%) as a colourless syrup; $[\alpha]_D^{25}$ +42.1 (*c* = 1.0, $CHCl_3$).

IR (film): 3533, 3070, 3049, 2932, 2886, 2858, 1740, 1472, 1428, 1380, 1254, 1221, 1170, 1109, 1006 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.86 [s, 9 H, $SiC(CH_3)_3$], 1.05 [s, 9 H, $SiC(CH_3)_3$], 1.40 (s, 3 H, CH_3 acetal), 1.41 (s, 3 H, CH_3 acetal), 3.12 (d, *J* = 3.3 Hz, 1 H, CHO*H*), 3.48 (dd, *J* = 9.3, 5.8 Hz, 1 H, C*H*$_a$H$_b$OBn), 3.70 (dd, *J* = 9.3, 8.0 Hz, 1 H, CH$_a$*H*$_b$OBn), 3.75–3.82 (m, 1 H, C*H*$_2$OTBDPS), 3.84–3.93 (m, 1 H, C*H*$_2$OTBDPS), 4.02 (dd, *J* = 6.3, 1.1 Hz, 1 H, H-6), 4.07–4.13 (m, 1 H, C*H*OH), 4.27 (dd, *J* = 1.9, 1.1 Hz, 1 H, H-4), 4.33 (ddd, *J* = 7.8, 5.8, 2.0 Hz, 1 H, C*H*OTBS), 4.43 (d, *J* = 11.8 Hz, 1 H, PhC*H*$_a$H$_b$), 4.51 (d, *J* = 11.8 Hz, 1 H, PhCH$_a$*H*$_b$), 7.27–7.69 (m, 15 H, 3 C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, –4.7 [$Si(CH_3)_2$], 18.1 8Si*C*$(CH_3)_3$], 19.1 [Si*C*$(CH_3)_3$], 23.6, 24.2 (CH_3 acetal), 25.7 [SiC(*C*$H_3)_3$], 26.7 [SiC(*C*$H_3)_3$], 61.2 (*C*H_2OTBDPS), 68.0 (CHOH), 70.1 (*C*H_2OBn), 71.2 (*C*HOTBS), 73.2 (Ph*C*H_2), 75.2 (C-6), 76.9 (C-4), 101.0 (acetal C), 127.5, 127.6, 128.2, 129.4, 129.6 (Ar-C), 133.4, 133.4 (Ar-C, *ipso*), 135.4 (Ar-C), 137.7 (Ar-C, *ipso*), 208.7 (C=O).

MS (CI): *m*/*z* (%) = 708.6 (1, MH^+), 707.7 (2, M^+), 395.3 (24), 337.2 (17), 314.3 (11), 313.2 (50), 236.2 (19), 235.2 (100), 205.1 (19).

HRMS (EI): *m*/*z* calcd for $C_{33}H_{41}O_5Si_2$ ($M^+ - C_7H_{17}O_2$), 573.2493; found, 573.2495.

Anal. Calcd for $C_{40}H_{58}O_7Si_2$ (707.1): C, 67.95; H, 8.27. Found C, 67.73; H, 8.72.

(*R*,*R*,*R*,*R*)-4-[2-Benzyloxy-1-(*tert*-butyldimethylsilanyloxy)ethyl]-6-(2-benzyloxy-1-hydroxyethyl)-2,2-dimethyl[1,3]dioxan-5-one (4f)

The boron enolate of ketone **3** (0.265 g, 0.67 mmol) was generated and reacted with freshly prepared benzyloxyacetaldehyde (0.24 mL, 1.71 mmol) according to the general procedure. Oxidative workup and subsequent flash chromatography on silica gel (eluent: 4:1 → 3:1 pentane–Et_2O) gave the title compound **4f** (0.216 g, 60%) as a colourless syrup; $[\alpha]_D^{26}$ +66.7 (*c* = 1.0, $CHCl_3$).

IR (film): 3540, 3064, 3031, 2987, 2930, 2858, 1744, 1497, 1456, 1378, 1252, 1223, 1169, 1100, 1029, 1007 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.86 [s, 9 H, $SiC(CH_3)_3$], 1.38 (s, 3 H, CH_3 acetal), 1.41 (s, 3 H, CH_3 acetal), 3.01 (d, *J* = 3.7 Hz, 1 H, CHO*H*), 3.47 (dd, *J* = 9.5, 5.8 Hz, 1 H, C*H*$_a$H$_b$OBn), 3.57–3.64 (m, 2 H, C*H*$_2$OBn), 3.69 (dd, *J* = 9.2, 7.9 Hz, 1 H, CH$_a$*H*$_b$OBn), 4.01–4.06 (m, 1 H, C*H*OH), 4.29–4.30 (m, 2 H, H-4,6), 4.33 (ddd, *J* = 7.8, 5.9, 1.9 Hz, 1 H, C*H*OTBS), 4.45 (d, *J* = 11.9 Hz, 1 H, PhC*H*$_a$H$_b$), 4.51 (d, *J* = 11.9 Hz, 1 H, PhCH$_a$*H*$_b$), 4.53 (d, *J* = 11.9 Hz, 1 H, PhC*H*$_a$H$_b$), 4.59 (d, *J* = 11.9 Hz, 1 H, PhCH$_a$*H*$_b$), 7.27–7.37 (m, 10 H, 2 C_6H_5).

^{13}C NMR (126 MHz, $CDCl_3$): δ = –4.9, –4.7 [$Si(CH_3)_2$], 18.1 [Si*C*$(CH_3)_3$], 23.6, 24.2 (CH_3 acetal), 25.7 [SiC(*C*$H_3)_3$], 69.7 (CHOH), 70.0, 70.1 (*C*H_2OBn), 71.4 (*C*HOTBS), 72.2 (C-4/6), 73.3, 73.5 (Ph*C*H_2), 77.0 (C-4/C-6), 101.3 (acetal C), 127.5, 127.6, 127.7, 127.7, 128.3, 128.3 (Ar-C), 137.9, 138.2 (Ar-C, *ipso*), 209.2 (C=O).

MS (CI): *m*/*z* (%) = 547.4 (11, MH^+ + 2), 546.4 (37, MH^+ + 1), 545.4 (100, MH^+), 527.3 (15, $MH^+ - H_2O$), 437.3 (12), 395.3 (8, MH^+ – BnOCH_2CHO), 133.1 (10).

HRMS (EI): *m*/*z* calcd for $C_{23}H_{29}O_6Si$ ($M^+ - C_7H_{15}O$), 429.1733; found, 429.1733.

Anal. Calcd for $C_{30}H_{44}O_7Si$ (544.8): C, 66.14; H, 8.14. Found C, 65.88; H, 8.02.

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