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 criteria. 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. Most of the research has focussed on aldol-type reactions of suitable glycolic acid derivatives. The aldol reaction of 2-(trimethylsilyloxy)furan and α-oxygenated aldehydes has also been utilised with success. 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. Paterson has employed chiral propionate- and lactate-derived protected α-hydroxy ketones in highly diastereoselective boron-mediated aldol reactions. Recently, Sasaki et al. made elegant use of a lactate-derived chiral α-hydroxy ketone in natural product synthesis. Alternatively, in new developments, the direct regioselective enolisation of unprotected α-hydroxy ketones has been demonstrated with biological catalysts as well as small organic promoters and bimetallic complexes. 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. 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 and in Mukaiyama aldol reactions of the Z-silyl enol ether of 1,3-di-O-benzylxoyacetone and the corresponding cyclohexylidene derivative. 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. 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 DHA 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. A conceptually similar bis-acetal erythulose derivative was employed by Carda and Marco et al. in boron-mediated aldol reactions. 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. More recent work has shown that the combination of prochiral ketone, chiral base and chiral aldehyde is essential for high enantioselectivity. 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

Abstract: A highly diastereo- and enantioselective entry to higher order ketopolys, 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.

Keywords: chiral dihydroxyacetone equivalent, α-substituted ketones, aldol reactions, polyols, asymmetric synthesis
SAMP or RAMP hydrazone.\(^{17}\) The azaenolate, generated by deprotonation with \(\text{i-BuLi}\) 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 benzaldehyde returned the \(1,2\)-syn diastereoisomer. However, the boron enolate of chiral DHA equivalent (\(\text{S}\)) readily available from the corresponding SAMP hydrazone reacted smoothly with a variety of aldehydes to give, after cleavage of the \(\alpha\)-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 systems.\(^{19}\)

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 concept. The synthesis of 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 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 precursor 3 in excellent yield. Slight epimerisation of the \(\alpha\)-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. Diastereomically pure 3 (\(\geq 96\%\) de), however, was obtainable by preparative HPLC.

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 \(\text{Cy}_2\text{BCl}\) (1.5 equiv) and \(\text{Et}_3\text{N}\) (1.7 equiv) in diethyl ether at low temperature (\(-78^\circ\)C) before warming to \(0^\circ\)C. The resulting boron enolate was recooled to \(-78^\circ\)C before a solution of the corresponding aldehyde (1.3 – 2.5 equiv) in diethyl ether was added and the reaction was stirred at \(-78^\circ\)C for 1 hour before warming to \(-24^\circ\)C. Subsequent oxidative workup (30% aq H\(_2\)O\(_2\), 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 (\(\geq 96\%\) 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 \(\text{Cy}_3\text{BOH}\). The lower yields of the reactions in some cases may reflect an increased sensitivity towards this oxidative workup.\(^{20}\)

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
Anhyd CH₂Cl₂ was distilled from CaH₂, MeOH was distilled from Mg, anhyd Et₂O and THF were distilled from Na/Pb alloy (benzenophenone indicator). Anhyd Et₂N was stored over and distilled from CaH₂. Anhyd H₂O was distilled from freshly purified aldehyde (1.3–2.5 equiv) in Et₂O (3 mL/mmol ketone) and extracted with CH₂Cl₂ (4 volumes). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated in vacuo to give the crude product as a colourless syrup. Purification by flash chromatography on silica gel (eluent: 97:3 CH₂Cl₂/MeOH) was carried out under pressure using Merck silica gel (400–630 mesh) and the access to both enantiomeric forms makes this approach attractive and flexible for polyhydroxylated natural product synthesis with which we are now engaged.

Reactions were carried out at r.t. under argon in predried glassware using anhyd solvents unless otherwise stated. Distilled H₂O was used. All aqueous solutions were saturated unless otherwise stated. Phosphate buffer (pH 7) was a solution of KH₂PO₄ (34.0 g) and NaOH (5.82 g) in H₂O (500 mL). Distilled solvents were used 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 F₂54) and visualised by ultra violet radiation (254 nm), acidic ammonium molybdate(V) or alkaline KMnO₄.

Optical rotations were measured with a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1760 spectrophotometer. ¹H and ¹³C 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 SSQ 7000 spectrometer (CI 100 eV; EI 70 eV) and high resolution mass spectra on a Finnigan SSQ 7000 spectrometer (CI 100 eV; EI 70 eV) and high resolution mass spectra on a Finnigan SSQ 7000 spectrometer (CI 100 eV; EI 70 eV) and high resolution mass spectra on a Finnigan SSQ 7000 spectrometer (CI 100 eV; EI 70 eV).

**Table**

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>[α]D19</th>
<th>de (%)</th>
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<td>a</td>
<td>Pr</td>
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<td>iPr</td>
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<td>f</td>
<td>CH₃OBn</td>
<td>60</td>
<td>+66.7</td>
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"Yields after chromatography."

"Measured at 26 ± 1.0 °C, c = 1.0, CHCl₃."

"Determined by ¹H and ¹³C NMR spectroscopy."

The boron enolate of ketone 3 (0.25 g, 0.66 mmol) was generated and reacted with freshly distilled n-butanol (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–Et₂O) gave the title compound 4a (0.189 g, 64%) as a colourless syrup; [α]D²⁶ +68.7 (c = 1.0, CHCl₃).

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, CDCl₃): δ = 0.06 (s, 3 H, SiCH₃), 0.10 (s, 3 H, SiCH₃), 0.87–0.89 [m, 12 H, SiC(CH₃)₃], 1.35 (s, 3 H, CH₃ acetal), 1.80 (CH₃), 1.87 (CH₃), 2.96 (d, J = 3.0 Hz, 1 H, CH₂O), 3.48 (dd, J = 9.2, 5.9 Hz, 1 H, CH₂OH), 3.66 (ap dt, J = 8.5, 3.0 Hz, 1 H, CH₂O), 3.71 (d, J = 9.2, 8.1 Hz, 1 H, CH₂OH), 4.04 (dd, J = 8.4, 1.0 Hz, 1 H, H-6), 4.29 (ap J = 1.8 Hz, 1 H, H-4), 4.34 (dd, J = 8.0, 0.0 Hz, 1 H, CHOCH₃), 4.46 (d, J = 11.8 Hz, 1 H, PhCH₂H), 4.52 (d, J = 11.8 Hz, 1 H, PhCH₂H), 7.26–7.36 (m, 5 H, C₆H₅).

11C NMR (100 MHz, CDCl₃): δ = −4.5, −4.3 [SiCH₃], 15.4 (CH₂CH₂), 18.5 [Si(CH₃)₃], 19.7 (CH₂CH₂), 24.8 (CH₃ acetal), 26.4 [Si(CH₃)₃], 28.7 [CH₂CH₂], 70.3 (CH₂OH), 71.8 (CH₂OH), 72.8 (C-6), 73.7 (PhCH₃), 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 (Cl): m/z (%) = 468.3 (24, MH+ + 1), 465.4 (83, MH+), 448.4 (20, MH+ + 1 – H₂O), 447.4 (66, MH+ – H₂O), 407.4 (15), 396.3 (28, MH+ + 1 – CH₂C(OH)CH₂), 395.3 (100, MH+ – CH₂C(OH)CH₂), 378.3 (10), 377.3 (40), 375.3 (31), 373.2 (33), 205.2 (12), 161.2 (28), 127.3 (19), 71.3 (39).

HRMS (EI): m/z calcd for C₉H₇O₃Si (M+ – CH₃OH), 352.2097; found, 352.2092.

Anal. Calcd for C₉H₇O₃Si (464.7): C, 64.62; H, 6.86. Found C, 64.70; H, 8.93.

(R, R, R, R)-4-[2-Benzoyloxy-1-(tert-butyldimethylsilyloxy)ethyl]-6-(1-hydroxy-2-methylpropyl)-2,2-dimethyl[1,3]dioxan-5-one (4d)

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: 10:1 pentane–Et₂O) gave the title compound 4d (0.231 g, 66%) as a colourless syrup; [α]D²⁶ +68.7 (c = 1.0, CHCl₃).

IR (film): 3553, 3064, 3033, 2987, 2952, 2929, 2989, 2857, 1737, 1496, 1447, 1454, 1406, 1383, 1376, 1363, 1324, 1308, 1252, 1224, 1200, 1170, 1103, 1052, 1029, 1006 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 0.07 (s, 3 H, SiCH₃), 0.10 (s, 3 H, SiCH₃), 0.88 [s, 9 H, Si(CH₃)₃], 1.14 (s, 3 H, CH₃ acetal), 1.32 (s, 3 H, CH₃ acetal), 3.49 (dd, J = 9.3, 6.2 Hz, 1 H, CH₂OH), 3.57 (d, J = 3.0 Hz, 1 H, CHOCH₃), 3.72 (dd, J = 9.2, 8.4 Hz, 1 H, CH₂OH), 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 (dd, J = 8.0, 5.9, 2.1 Hz, 1 H, CHOCH₃), 4.45 (d, J = 12.1 Hz, 1 H, PhCH₂H), 4.52 (d, J = 11.8 Hz, 1 H, PhCH₂H), 4.77 [dd, J = 8.2, 2.7 Hz, 1 H, CHOH], 7.25–7.38 (m, 10 H, 2 C₆H₅).
(R,R,R,R)-4-[2-Benzoxyl-1-(tert-butyldimethylsilanyloxy)ethyl]-6-[3-(tert-butyldiphenylsilyloxy)-1-hydroxypropyl]-2,2-dimethyl[1]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-butyldimethyl)silylpropionamide (0.26 mL, 0.82 mmol) according to the general procedure. Subsequent workup and flash chromatography on silica gel (eluent: 9:1 CH2Cl2/MeOH) gave the title compound 4e as a colourless syrup; [α]25° +42.1 (c 1.0, CHCl3).

Acknowledgements

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References


(19) The one-pot bis-aldol reaction of 2,2-dimethyldioxan-5-one by enolisation, reaction with PhCHO, a second enolisation and then reaction with CyCHO was recently reported. The racemic anti-trans-anti product was isolated in 64% yield. See Ref.11.

(20) Dimethyldioxirane has been proposed as an alternative oxidising agent in these systems. See Ref.11.


(22) For an alternative procedure from allyl alcohol, see: Arndt, H. C.; Carroll, S. A. Synthesis 1979, 202.