Chiral Dihydroxyacetone Equivalents in Synthesis: Rapid Assembly of Styryl 1,2-Polyols as an Entry to the Styryllactone Family of Natural Products

Dieter Enders,* Stuart J. Ince, Melanie Bonnekessel, Jan Runsink, Gerhard Raabe

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Straße 1, 52074 Aachen, Germany
Fax +49(241)8092127; E-mail: Enders@RWTH-Aachen.de

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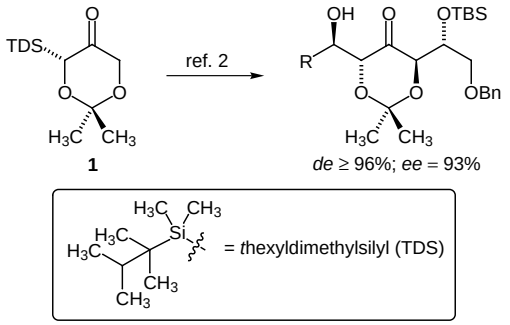
Abstract: A rapid entry to the polyol framework of the styryllactone family of natural products is reported. The key steps are two highly diastereoselective boron-mediated aldol reactions of a chiral dihydroxyacetone equivalent followed by a 1,3-*anti* or 1,3-*syn*-selective reduction. In addition, Evans–Tishchenko reduction of the cyclic aldol products effected an equilibration to the 1,2-*syn* aldol product before 1,3-*anti* selective reduction.

Key words: α-silyldioxanone, aldol reactions, cyclic ketone reduction, Evans–Tishchenko, styryllactones, asymmetric synthesis

Chiral dihydroxyacetone derivatives have proved to be excellent building blocks for polyhydroxylated natural product synthesis.[1] Recently, we described the application of bis-aldol methodology to α-silyldioxanone **1** resulting in a diastereo- and enantioselective entry to differentially protected higher order ketopolyols (Scheme 1).[2] Having established the feasibility of this approach we turned towards natural product synthesis. The styryllactone family is typified by mono- or bicyclic tetrahydrofuran ring systems, densely decorated with oxygenated stereocentres, often exhibiting useful levels of antitumour activity.[3–5] Gonioheptolide A (**2**)[6] is an unusual member of this family of natural products, in that the usual lactone moiety has been converted to the corresponding methyl ester. Nevertheless, it displays moderate antitumour activity against a variety of human tumour cell lines and we decided to apply our extended methodology to its total synthesis. Towards this goal we first investigated the enantio- and diastereoselective synthesis of an open-chain polyol precursor as proof of concept.



Scheme 1

The retrosynthetic plan for the synthesis of these 1,2-styryl polyols hinges on the use of a single auxiliary stereogenic centre to build up five contiguous oxygenated stereocentres (Scheme 2). Our initial disconnections of gonioheptolide A were to mask the ester as a protected alcohol and to disconnect the tetrahydrofuran ring. In the forward sense this would correspond to the attack of an oxyanion at the benzylic position on a tosylate leaving group, followed by adjustment of the oxidation level.

We considered the thus required linear hexaol to be readily accessible via a 1,3-*anti* or 1,3-*syn* selective reduction of a suitably protected hydroxyketone. The stereochemistry of these hydroxyketones would then be induced through our recently developed asymmetric bis-aldol methodology from α-silyldioxanone **1**, in which the boron enolates of α-chiral dioxanones reacted in a very selective 1,2- and 1,3-*anti* fashion with a variety of aldehydes.[2]

In this paper we report the development of an efficient route to the required 1,2-polyol framework of gonioheptolide A via two asymmetric aldol reactions and a directed ketone reduction. A critical factor in this study proved to be the selection of a suitable diastereoselective reducing agent.

A challenging aspect of polyol synthesis is to minimise the number of protecting group manipulations. In this respect the Evans–Tishchenko reduction[7] was considered the perfect choice for the directed reduction as it would introduce a benzoate at the benzylic position. Cleavage of the ester followed by cyclisation of the resulting anion onto the tosylate could then be carried out in one synthetic operation.

β-Silyloxyketone **3**[8] was prepared in three steps from the α-silylketone **1**[9] in 65% overall yield (Scheme 3). Reaction of the corresponding boron enolate with benzaldehyde gave the diastereopure hydroxyketone **4** in good yield (84%). Next we turned to introducing the fifth and final stereocentre. Evans–Tishchenko reduction of **4** under the standard conditions gave hydroxybenzoate **5** in 95% yield (Scheme 3). The relative stereochemistry could not be proven by NMR due to significant signal overlap. Subsequent desilylation, however, gave crystalline triol **6** (Figure). Single crystal X-ray analysis (Scheme 3) proved the structure to be the 1,2-*syn*-1,3-*anti*-diastereoisomer and not the 1,2-*anti*-1,3-*anti*-diastereoisomer as required.[10]

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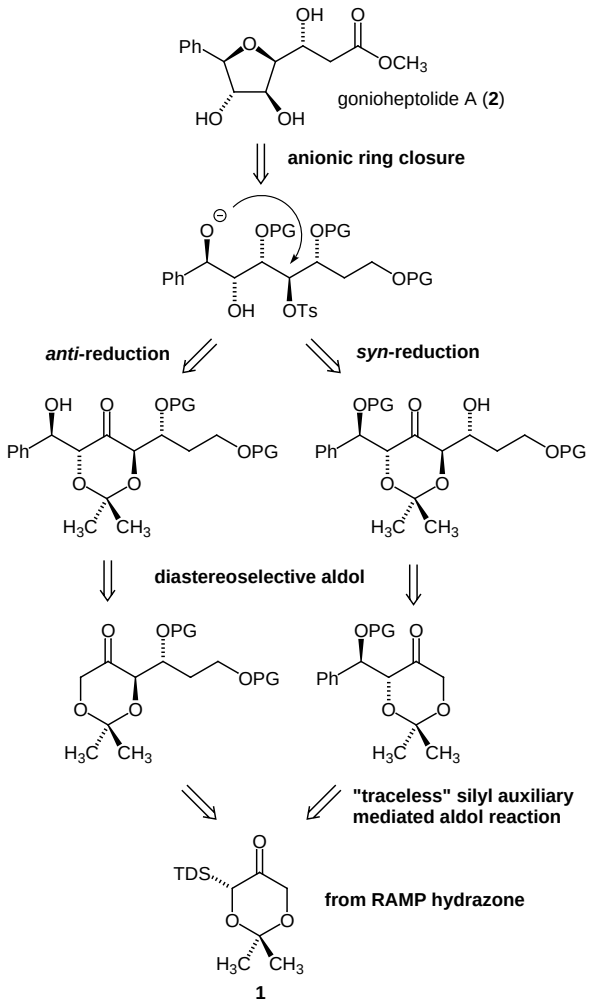


Scheme 2

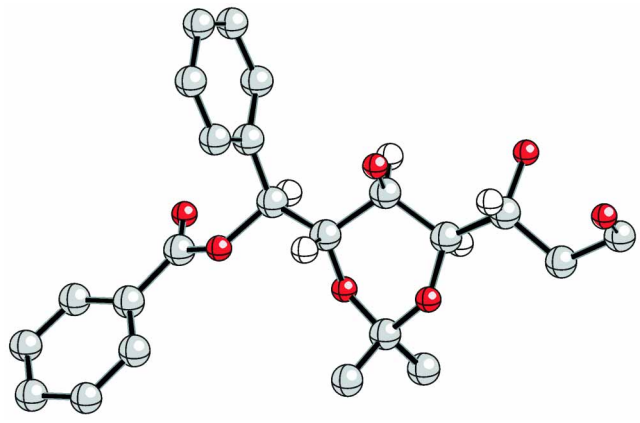
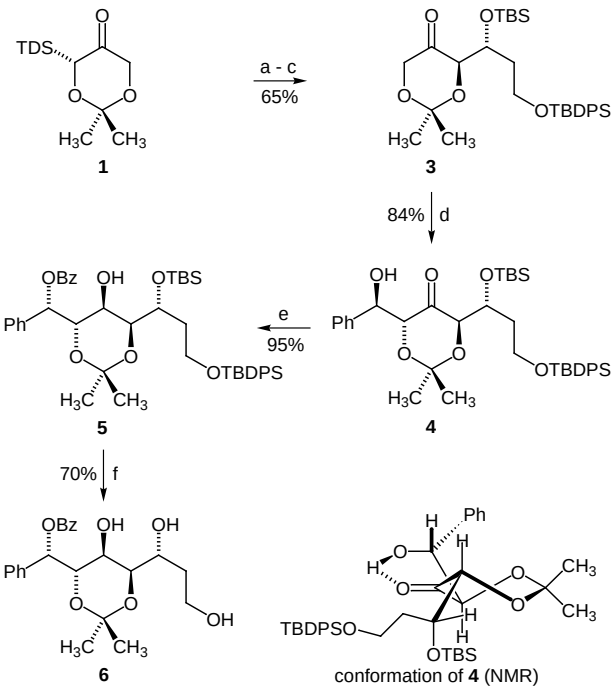


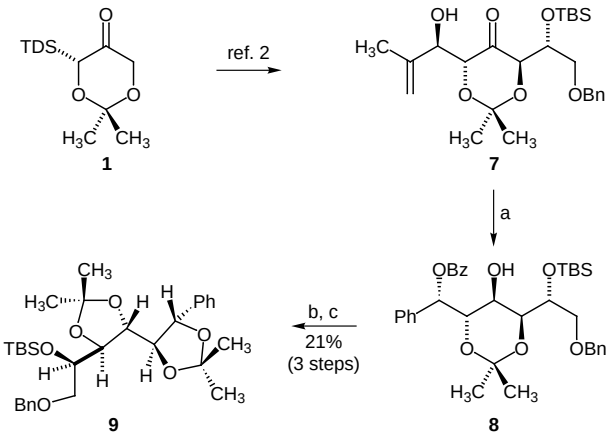
Figure X-ray structure of **6**.

The diastereomeric result of the Evans–Tishchenko reduction is the result of a Sm-catalysed equilibration process as previously reported for the Tishchenko reaction of cyclohexanone and benzaldehyde.[11–13] Further proof of this dissociative mechanism was provided by reduction of hydroxyketone **7**[2] (Scheme 4). The only observed product



Scheme 3 *Reagents and conditions*: (a) Cy_2BCl, Et_3N, Et_2O, –78 to 0 ºC, then $TBDPSO(CH_2)_2CHO$, Et_2O, –78 to –24 ºC. (b) $Et_3N{\cdot}3$ HF, THF, –20 ºC. (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 ºC. (d) Cy_2BCl, Et_3N, Et_2O, –78 ºC to 0 ºC, then PhCHO, Et_2O, –78 to –24 ºC. (e) SmI_2 (0.6 equiv), PhCHO (8 equiv), THF, 0 ºC. (f) TBAF, THF. (TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl).

was the phenyl substituted derivative **8** in which methallyl aldehyde had dissociated and the resulting (postulated) Sm enolate was trapped with excess PhCHO. The stereochemistry was assigned by derivatisation as the bis-acetal **9**.



Scheme 4 *Reagents and conditions*: (a) SmI_2, PhCHO, THF, 0 ºC. (b) K_2CO_3, MeOH. (c) DMP, CSA (cat.), CH_2Cl_2.

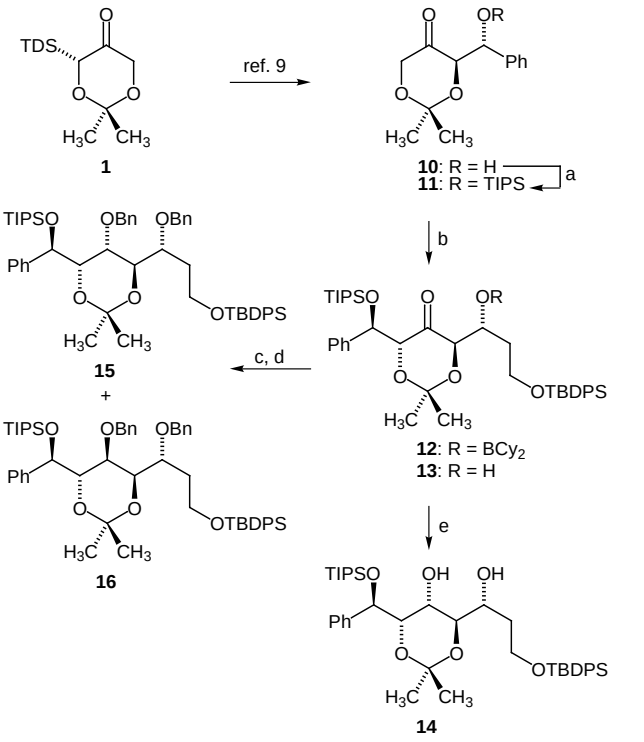
These reduction products are formally derived from a *syn*-selective aldol reaction between a cyclic ketone and an aldehyde. If this reaction could be generalised for a range of aldehydes, it offers a route to natural products containing

cyclic substructures previously unattainable by contemporary aldol methodology.

To forward the total synthesis it was decided to exploit the symmetry of the dioxanone system and reverse the order of the aldol reactions, thus requiring a 1,3-*syn* reduction to install the fifth stereocentre. Furthermore, preliminary experiments on **5** had not been successful in deprotecting the acetal without significant 2º OTBS deprotection as well.[14] In view of this the tri-*iso*-propylsilyl (TIPS) group was chosen as a more acid stable alternative.

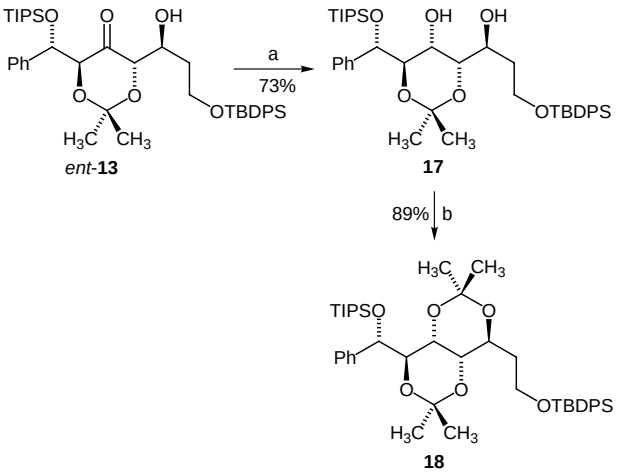
The second generation synthesis started with hydroxyketone **10**[15] prepared in 59% yield from α-silyldioxanone **1** (Scheme 5). TIPS protection with TIPSOTf and 2,6-lutidine returned **11** quantitatively although with a significant amount of α-epimerisation (de = 73%). The resulting *syn*/*anti* mixture could not be separated by HPLC. In an attempt to effect the aldol reaction and reduction in one-pot Paterson's conditions were used.[16] Thus, the aldol reaction between the boron enolate of ketone **11** and 3-(*tert*-butyl-diphenyl-silanyloxy)-propionaldehyde[17] was quenched at –78 ºC with $LiBH_4$. Subsequent oxidative (H_2O_2) work up and chromatography yielded a near 1:1 inseparable mixture of the 1,3-*syn* diol **14** and its *trans* isomer, together with the corresponding minor diastereoisomers, in quantitative yield. NMR analysis of this mixture revealed that the aldol reaction itself proceeded with complete diastereoselection as expected. Upon benzylation the two major diastereomers could be separated by chromatography to give 1,3-*syn* **15** and 1,3-*trans* **16** in 35% and 33% yield, respectively. A range of boron hydride sources was then screened on both enantiomers of ketone **13**.[18] $Me_4NBH(OAc)_3$,[19] which had shown *syn* selectivity in the reduction of a 4-(hydroxybenzyl)-1,3-dioxan-5-one,[20] proved unreactive. L-Selectride®, which had proven selective in earlier dioxanone work[1e,g] and $BH_3{\cdot}SMe_2$[21] proved only poorly *syn* selective (yields 67–78%; 0–17% reduction de). Our breakthrough came with $Zn(BH_4)_2$[22] which, in a small scale trial experiment, delivered the *syn*-diol **14**[28] in 71% yield and excellent 85% reduction de. On scale up (6 mmol) the *syn*-diol **14** was afforded in 52% ds (74% reduction de) and excellent yield (87% over 2 steps from ketone **13**). Separation of the diastereoisomers was again possible after benzylation (not shown). In contrast to the usual $Zn(BH_4)_2$ mediated reductions it was necessary to warm the reaction to room temperature to ensure complete reduction. Furthermore, simply quenching the reaction with the minimum quantity of water, filtration of the resulting suspension through Celite® and a subsequent base wash was found to be the optimal work up procedure.

Interestingly, Evans' catechol borane/Rh(I) system[23] returned 73% of the *anti* diol **17** in 72% reduction de (Scheme 6). The stereochemistry was proven by derivatisation as the bis-acetal **18**. The diastereoselectivity of reduction of a variety of 4,6-disubstituted 1,3-dioxan-5-ones has been investigated both theoretically and experimentally.[24–26] We tentatively assign the *anti* selectivity to



Scheme 5 *Reagents and conditions*: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, –78 to 0 ºC, quant. (de = 73%). (b) Cy_2BCl, Et_3N, Et_2O, –78 ºC to 0 ºC, then $TBDPSO(CH_2)_2CHO$, Et_2O, –78 to –24 ºC. (c) $LiBH_4$, THF/Et_2O, –78 ºC, quant. (d) NaHMDS, BnBr, TBAI (cat.), THF, 0 ºC to r.t., **15** 35%, **16** 33% (from **11** via **12**). (e) $Zn(BH_4)_2$, Et_2O, –78 ºC to r.t., 87% (from **11**).

an intermolecular hydride delivery via the corresponding boron chelate.[27] The *syn* products are the result of pseudo-axial attack of hydride. It is likely that the increase in selectivity in the case of $Zn(BH_4)_2$ is a result of chelation to one or more of the dioxanone oxygen atoms, especially as $Zn(BH_4)_2$ is well known to favour 5-ring over 6-ring chelates. Further work is clearly needed to clarify the exact nature of reduction in these dioxanone systems.



Scheme 6 *Reagents and conditions*: (a) Catechol borane, $(Ph_3P)_3RhCl$ (cat.), THF, –10 ºC. (b) DMP, CSA (cat.), CH_2Cl_2.

In summary, the combination of diastereoselective aldol reactions of our chiral dihydroxyacetone equivalent and diastereoselective reductions offer a competitive route to the open-chain polyol precursors of styryllactone derivatives. The symmetry of the dioxanone system proved particularly useful in allowing a reversal of the order of aldol reactions. By choice of reducing agent either 1,3-*syn* and 1,3-*anti* selectivity was attainable. We also discovered that the Evans–Tishchenko reduction applied to dioxanone systems gives the formal products of a 1,2-*syn* selective aldol reaction and a 1,3-*anti* selective reduction, proving to be an entry to usually unattainable reaction products. To conclude, the development of an enantio- and diastereoselective synthesis of the required 1,2-polyol framework of gonioheptolide A (**2**) has opened the way to a total synthesis which will be reported in due course.

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References

(1) (a) Ulven, T.; Carlsen, P. H. J. *Eur. J. Org. Chem.* **2001**, 3367. (b) Majewski, M.; Nowak, P. *J. Org. Chem.* **2000**, *65*, 5152. (c) Doyle, M. P.; Tedrow, J. S.; Dyatkin, A. B.; Spaans, C. J.; Ene, D. G. *J. Org. Chem.* **1999**, *64*, 8907. (d) Enders, D.; Hundertmark, T. *Eur. J. Org. Chem.* **1999**, 751. (e) Enders, D.; Prokopenko, O. F. *Liebigs. Ann.Chem.* **1995**, 1185. (f) Enders, D.; Whitehouse, D. L.; Runsink, J. *Chem.–Eur. J.* **1995**, *1*, 382. (g) Enders, D.; Jegelka, U. *Tetrahedron Lett.* **1993**, *34*, 2453. (h) Enders, D.; Jegelka, U.; Dücker, B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 423. (i) Enders, D.; Jegelka, U. *Synlett* **1992**, 999. (j) Hirama, M.; Noda, T.; Itô, S. *J. Org. Chem.* **1988**, *53*, 708.

(2) Enders, D.; Ince, S. J. *Synthesis* **2002**, 619.

(3) For a review of structure and activity see: Blázquez, M. A.; Bermejo, A.; Zafra-Polo, M. C.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 161.

(4) For selected total syntheses see: (a) Bermejo, A.; Tormo, J. R.; Cabedo, N.; Estornell, E.; Figadère, B.; Cortes, D. *J. Med. Chem.* **1998**, *41*, 5158. (b) Bermejo, A.; Blázquez, M. A.; Serrano, A.; Zafra-Polo, M. C.; Cortes, D. *J. Nat. Prod.* **1997**, *60*, 1338. (c) Bruns, R.; Wernicke, A.; Koll, P. *Tetrahedron* **1999**, *55*, 9793. (d) Chen, W.-P.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 103. (e) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3125. (f) Friesen, R. W.; Bissada, S. *Can. J. Chem.* **1998**, *76*, 94. (g) Gracza, T.; Szolcsanyi, P. *Molecules* **2000**, *5*, 1386. (h) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161. (i) Mereyala, H. B.; Gadikota, R. R. *Indian J. Chem., Sect. B.* **2000**, *39*, 166. (j) Mukai, C.; Hirai, S.; Hanaoka, M. *J. Org. Chem.* **1997**, *62*, 6619. (k) Paddon-Jones, G. C.; Hungerford, N. L.; Hayes, P.; Kitching, W. *Org. Lett.* **1999**, *1*, 1905. (l) Shing, T. K. M.; Tsui, H.-C.; Zhou, Z.-H. *J. Org. Chem.* **1995**, *60*, 3121. (m) Su, Y. L.; Yang, C. S.; Teng, S. J.; Zhao, G.; Ding, Y. *Tetrahedron* **2001**, *57*, 2147. (n) Surivet, J.-P.; Vatèle, J.-M. *Tetrahedron* **1999**, *55*, 13011. (o) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493. (p) Yang, M.; Li, H. M.; Zhao, G.; Yu, Q. S.; Ding, Y. *Chin. J. Chem.* **2000**, *18*, 225. (q) Yang, Z. C.; Zhou, W. S. *Heterocycles* **1997**, *45*, 367. (r) Ye, J. H.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1993**, *34*, 8007. (s) Yi, X. H.; Meng, Y.; Hua, X. G.; Li, C. J. *J. Org. Chem.* **1998**, *63*, 7472.

(5) For analogue synthesis see: (a) Bermejo, A.; Léonce, S.; Cabedo, N.; Andreu, I.; Caignard, D. H.; Atassi, G.; Cortes, D. *J. Nat. Prod.* **1999**, *62*, 1106. (b) Li, H. M.; Yang, M.; Zhou, G.; Yu, Q. S.; Ding, Y. *Chin. J. Chem.* **2000**, *18*, 388. (c) Mereyala, H. B.; Gadikota, R. R.; Joe, M.; Arora, S. K.; Dastidar, S. G.; Agarwal, S. *Biorg. Med. Chem. Lett.* **1999**, *7*, 2095. (d) Peris, E.; Estornell, E.; Cabedo, N.; Cortes, D.; Bermejo, A. *Phytochemistry* **2000**, *54*, 311. (e) Shing, T. K. M.; Tai, V. W. F. *J. Org. Chem.* **1999**, *64*, 2140.

(6) (a) For isolation see: Fang, X.-P.; Anderson, J. E.; Qiu, X.-X.; Kozlowski, J. F.; Chang, C.-J.; McLaughlin, J. L. *Tetrahedron* **1993**, *49*, 1563. (b) For semisynthesis and structure revision see: Mukai, C.; Yamashita, H.; Hirai, S.; Hanaoka, M.; McLaughlin, J. L. *Chem. Pharm. Bull.* **1999**, *47*, 131.

(7) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

(8) All new compounds gave consistent analytical data including correct elemental analysis and/or HRMS.

(9) Enders, D.; Prokopenko, O. F.; Raabe, G.; Runsink, J. *Synthesis* **1996**, 1095.

(10) CCDC 179448 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax:+44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

(11) Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 843.

(12) In contrast, the reaction of α-silyl ketone **1** with SmI_2 and PhCHO, according to the conditions described for cyclohexanone in ref.[11], was very sluggish and poorly diastereoselective.

(13) NMR analysis of ketone **4** confirms it to be in a twist-boat conformation. In this respect a discussion of the reduction selectivity is complicated, as true axial or equatorial attack is no longer applicable in a twist-boat system. Pseudoaxial attack seems possible for both the *syn*- and *anti*-aldol products, the latter case may be disfavoured due to the proximity of the electron rich aryl ring and the coordinating Sm species.

(14) A range of protic and Lewis acidic hydrolyses, transketalisations and thioketalisation were unsuccessful giving starting material or inseparable mixtures of TBS/acetal deprotection. It is possible that the C-5 alcohol is acting as a general acid.

(15) (*S*,*S*)-**10**: See ref.[9]

(16) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811.

(17) Prepared in two steps from propane-1,3-diol (silylation, Dess–Martin oxidation). Purified by chromatography on silica gel before use.

(18) Analytical HPLC (chiral stationary phase) showed that the ee of **1** was carried through to the reduction products with no depreciation. **1** was prepared in up to 96% ee as judged by GC (chiral stationary phase).

(19) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(20) Hundertmark, T. *Dissertation*; RWTH: Aachen, **2000**.

(21) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3734.

(22) For a review of use in directed reductions see: Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338.

(23) Evans, D.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190.

(24) For several theoretical models of substituted 1,3-dioxan-5-ones see: (a) Artau, A.; Ho, Y.; Kenttämaa, H.; Squires, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 7130. (b) Wu, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 10993.

(25) For a related examination of substituted 1,3-dioxanes see: Cieplak, P.; Howard, A. E.; Powers, J. P.; Rychnovsky, S. D.; Kollman, P. A. *J. Org. Chem.* **1996**, *61*, 3662.

(26) For reductions of 4-mono- and 4,6-bis-alkylated 1,3-dioxan-5-ones see: Enders, D.; Kownatka, D.; Hundertmark, T.; Prokopenko, O. F.; Runsink, J. *Synthesis* **1997**, 649; and references 1a–e and 1g.

(27) In this case the much smaller ligands on boron may make chelate formation much easier. The observed colour change of the reaction, from red to yellow, is consistent with H_2 transfer to the Rh(I) catalyst. On closer examination of a model there would appear to be more steric crowding on the lower face of the chelated complex, consistent with the observed outcome.

(28) Preparation of 1,3-*syn* diol **14** (over 2 steps from ketone **11**): To a stirred solution of Cy_2BCl[29] (2.0 mL, 9.0 mmol, 1.5 equiv) in anhyd Et_2O (50 mL) at –78 ºC, under an Ar atmosphere, was sequentially added freshly distilled Et_3N (1.42 mL, 10.2 mmol, 1.7 equiv) and a solution of ketone **11** (2.35 g, 6.0 mmol, 1.0 equiv, de = 73%) in anhyd Et_2O (20 mL) dropwise via syringe. Stirring was continued at –78 ºC for a further 20 min before warming to 0 ºC for 1 h. The resulting bright yellow suspension was recooled to –78 ºC and a solution of freshly prepared 3-(*tert*-butyl-diphenyl-silanyloxy)-propionaldehyde (3.45 g, 11.0 mmol, 1.8 equiv) in anhyd Et_2O (10 mL) was added dropwise via syringe. Stirring was continued at –78 ºC for a further 90 min before the flask was sealed and allowed to stand in a freezer (–24 ºC) for 10 h. The reaction was quenched with phosphate buffer (pH 7, 120 mL) and extracted. The aq layer was extracted with Et_2O and the combined organic portions were concentrated in vacuo. The oily residue was resuspended in phosphate buffer (pH 7, 36 mL) and MeOH (36 mL) and cooled to 0 ºC. Aq H_2O_2 solution (30%, 18 mL) was added dropwise and the mixture stirred vigorously for a further 1 h. The mixture was poured into phosphate buffer (pH 7, 120 mL) and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic portions were washed with H_2O (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give a colourless oil. Purification by chromatography on silica gel (gradient elution: 19:1 → 8:1 pentane:Et_2O) gave the title compound **13** (4.94 g, de = 74%) heavily contaminated with aldehyde. An analytical sample (de = 74%) was afforded by further chromatography; $[\alpha]^{25}_D$ +58.9 (*c* 1.0 in $CHCl_3$); IR (thin film): 3543, 3071, 3050, 3032, 2942, 2891, 2866, 1739, 1472, 1464, 1428, 1383, 1219, 1169, 1112, 1068, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96–1.08 (m, 30 H, CH TIPS, CH_3 TIPS and TBDPS), 1.33 (s, 3 H, CH_3 acetal), 1.41 (s, 3 H, CH_3 acetal), 1.66–1.74 (m, 1 H, CH_aH$_b$), 1.75–1.82 (m, 1 H, CH$_a$$H_b$), 3.15 (d, 1 H, *J* = 3.3 Hz, (CHO*H*), 3.72 (dd, 1 H, *J* = 5.9, 1.0 Hz, H-4), 3.74–3.88 (m, 1 H, CH_2OTBDPS), 4.06–4.12 (m, 1 H, C*H*OH), 4.46 (dd, *J* = 2.8, 1.0 Hz, 1 H, H-6), 5.28 (d, *J* = 2.8 Hz, 1 H, (CH(OTIPS)), 7.20–7.67 (m, 15 H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5 (Si*C*H(CH_3)$_2$), 18.1, 18.2 (SiCH(*C*H$_3$)$_2$), 19.4 (Si*C*(CH_3)$_3$), 24.0, 24.3 (CH_3 acetal), 27.1 (SiC(*C*H$_3$)$_3$), 34.6 (CH_2), 61.6 (CH_2OTBDPS), 68.6 (*C*HOH), 74.4 (CH(OTIPS)), 76.1 (C-4); 80.0 (C-6), 101.5 (acetal C), 127.7, 127.8, 127.9, 128.0, 129.9, 130.0, (Ar-C), 133.7, 133.8 (Ar-C, *ipso*), 135.8 (Ar-C), 140.2 (Ar-C, *ipso*), 209.5 (C=O); MS (CI): *m/z* (%)= 350(4), 349(16), 313(56), 263(100), 235(62), 175(13); HRMS (EI): *m/z* calcd for $C_{19}H_{29}O_4Si$ [$M^+ - C_{22}H_{31}O_2Si$]: 349.1835. Found: 349.1835. Anal. Calcd for $C_{40}H_{60}O_6Si$ (705.08): C, 69.84; H, 8.85. Found: C, 69.29; H, 8.60.
To a stirred suspension of $NaBH_4$ (2.70 g, 70 mmol, 2.0 equiv) in anhyd Et_2O (210 mL) under an Ar atmosphere, at r.t., was added a solution of $ZnCl_2$ in Et_2O (Aldrich, 1.0 M, 35 mL, 35 mmol, 1.0 equiv) via syringe. The resulting white suspension was stirred for a further 2 d before allowing the precipitate to settle. The resulting clear supernatant solution of $Zn(BH_4)_2$ in Et_2O (ca. 0.14 M) was cooled to –78 ºC.
To a stirred solution of the crude ketone **13** (4.21 g, ca 5.97 mmol, 1.0 equiv) at –78 ºC, under an Ar atmosphere, was added the chilled supernatant solution of $Zn(BH_4)_2$ in Et_2O (ca 240 mL, ca 34 mmol, 5.6 equiv), via double-ended needle over 45 min. The reaction mixture was warmed very slowly to r.t. The reaction mixture was quenched after 24 h with H_2O until effervescence ceased (ca 5 mL) and stirred vigorously for 1 h. The resulting white suspension was filtered through Celite® and the filter-cake washed thoroughly with Et_2O (400 mL). The combined filtrates were washed with sat. aq $NaHCO_3$ solution and the aq portion back-extracted with Et_2O (200 mL). The combined organic portions were dried (Na_2SO_4), filtered and concentrated in vacuo to give a cloudy colourless oil. Purification by chromatography on silica gel (gradient elution: 6:1 → 1:1 pentane:Et_2O gave the title compound **14** (3.67 g, 87%, 52% ds, 74% de for reduction). On smaller scales a reduction de of 85% could be achieved; IR (thin film): 3472, 3071, 3050, 3031, 2943, 2892, 2866, 1471, 1463, 1428, 1380, 1224, 1198, 1172, 1112, 1069, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95–1.10 (m, 30 H, CH TIPS, CH_3 TIPS and TBDPS), 1.21 (s, 3 H, CH_3 acetal), 1.39 (s, 3 H, CH_3 acetal), 1.70–1.81 (m, 2 H, CH_2), 3.14 (d, 1 H, *J* = 2.5 Hz, CHO*H*), 3.59 (ap t, 1 H, *J* = 5.5 Hz, H-4), 3.70 (dd, *J* = 4.7, 3.0 Hz, 1 H, H-6), 3.78–3.90 (m, 2 H, CH_2OTBDPS), 3.92–3.97 (m, 1 H, C*H*OH), 4.09–4.13 (m, 1 H, H-5), 4.45 (d, 1 H, *J* = 3.6 Hz, 5-OH), 5.16 (d, 1 H, *J* = 4.7 Hz, CH(OTIPS)), 7.24–7.46 (m, 10 H, Ar-H), 7.63–7.67 (m, 5 H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.7 (Si*C*H(CH_3)$_2$), 18.2 (× 2) (SiCH(*C*H$_3$)$_2$, 19.4 (Si*C*(CH_3)$_3$), 24.1, 25.5 (CH_3 acetal), 27.2 (SiC(*C*H$_3$)$_3$), 34.5 (CH_2), 63.2 (CH_2OTBDPS), 69.7 (C-5), 72.4 (CHOH), 73.8 (C-6), 77.7 (CH(OTIPS)), 78.6 (C-4), 101.3 (acetal C), 127.1, 127.9 (× 2), 128.3 (× 2), 130.0 (Ar-C), 133.2, 133.3 (Ar-C, *ipso*), 135.7, 135.8 (Ar-C)], 141.3 (Ar-C, *ipso*); MS (CI): *m/z* (%) = 709(9) [MH^+ + 1], 534(54), 476(41), 458(29), 235(10), 175(100), 163(15); HRMS (EI): *m/z* calcd for $C_{38}H_{55}O_6Si_2$ [$M^+ - C_3H_7$]: 663.3537. Found: 663.3534.

(29) Prepared from the hydroboration of freshly distilled cyclohexene with monochloroborane dimethyl sulfide complex (Aldrich). For a procedure see: Cowden, C. J.; Paterson, I. In *Organic Reactions*, Vol. 51; Paquette, L. A., Ed.; Wiley: New York, **1997**, 1.