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Aldol Reactions with Erythrulose Derivatives: Stereoselective Synthesis of Differentially Protected *syn*-α,β-Dihydroxy Esters

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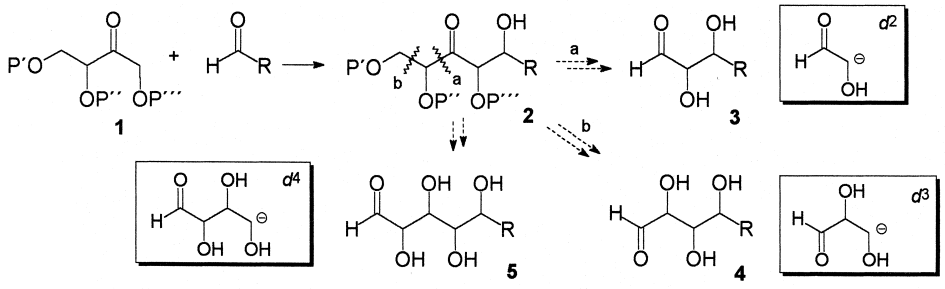
Abstract—Boron enolates of 1-*O*-silylated erythrulose 3,4-acetonides prepared with Brown's chloro-dicyclohexylborane/tertiary amine system have been shown to react with achiral aldehydes in a highly stereoselective way to yield a 1,2-*syn*/1,3-*syn* stereoisomer. Through oxidative cleavage of the aldol adducts with periodic acid hydrate, enantiopure *syn*-α,β-dihydroxy esters with either hydroxyl group differently protected have been prepared. These erythrulose derivatives therefore behave as a chiral hydroxy acetate (glycolate) enolate equivalent.

The aldol reaction[1] has proven to be a powerful and general method for the stereocontrolled construction of carbon–carbon bonds and has relevant application in the synthesis of natural polyoxygenated molecules such as macrolide and polyether antibiotics.[2] In connection with our current interest in the development of erythrulose as a useful C_4-chiral building block for the stereocontrolled construction of polyfunctionalized structures,[3] we envisaged the enolization of protected L-(*S*)-erythrulose derivatives 1 (P′, P″, P‴=protecting groups) and the subsequent addition of the resulting enolates to aldehydes. As shown in Scheme 1, though synthetic equivalents of the d^2 synthon hydroxy acetaldehyde enolate or its equivalent, the hydroxy acetic (glycolic) acid enolate, have been described,[4,5] there are no counterparts for the d^3 synthon α,β,-dihydroxy propanal homoenolate equivalent.[6] Furthermore, **1** could also act as an α,β,γ-trihydroxy butanal bishomoenolate equivalent (cf. **5**). In such a process, **1** would function as a hitherto unprecedented d^4 synthon type with no loss of carbon, thus maximizing atom economy.[7] The synthetic utility of erythrulose is therefore based on the fact that it may behave, according to convenience, as a C_4 chiral d^2, d^3 or d^4 synthon.



Scheme 1.

further manipulation of the key aldol adduct **2** through prior carbonyl reduction and selective cleavage of bonds *a* or *b* would yield selectively protected α,β-dihydroxy aldehydes **3** or α,β,γ-trihydroxy aldehydes **4**, respectively. Even

With this idea in mind, we have investigated L-(*S*)-erythrulose 3,4-acetonide derivatives **6** bearing three different silyl protecting groups (R=TES, TBS and TBDPS).[8] After initial failures with several enolate types,[9] we were eventually successful through the use of the Brown dicyclohexylboron chloride (Chx_2BCl)/tertiary amine system.[10] Aldol reactions promoted by this reagent mixture led to aldol adducts **7** in good chemical yields as an essentially single diastereoisomer (diastereomeric ratio, d.r.>95:5, as determined by ^1H and ^{13}C NMR; 12 out of the 18 possible R/R′

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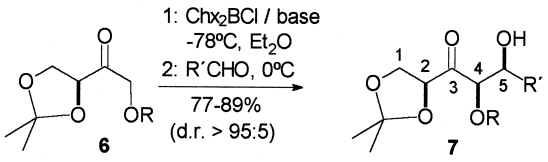


Scheme 2. R=TES, TBS, TBDPS. **7**: **a** R′=Et; **b** R′=*i*Pr; **c** R′=Ph; **d** R′=4-ClC_6H_4; **e** R′=4-$NO_2C_6H_4$; **f** R′=CH_2=C(Me).

combinations in Scheme 2 were prepared, see Experimental). Almost identical results were observed with all three silyl protecting groups using three different tertiary amines (Me_2NEt, Et_3N and iPr_2NEt) in three different solvents (Et_2O, THF and CH_2Cl_2). The sterically hindered pivaldehyde was the only aldehyde tested which did not react under the conditions described.[11,12]

The 2,4-*syn*/4,5-*syn* relative as well as the absolute configuration of the obtained aldol adducts was unequivocally established by X-ray diffraction analysis of the enantiomer of **7d** (R=TBS) and by a chemical correlation in the case of **7b** (R=TBS).[11,12] In this paper, we give detailed reaction conditions of the aforementioned aldol additions and complete physical and spectral data of the aldol adducts. Furthermore, we show that, as anticipated in our first communication,[11] erythrulose derivatives such as **6** behave as an effective chiral equivalent of the d^2 hydroxy acetic (glycolic) acid enolate synthon. Our aldol methodology therefore represents a useful tool in stereoselective organic synthesis.

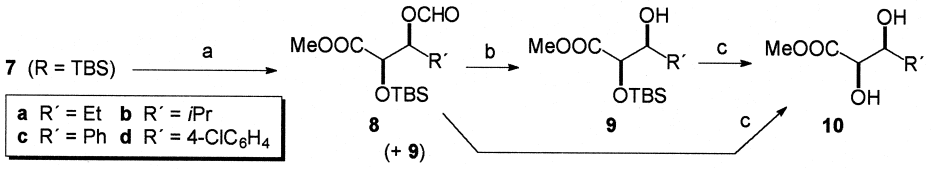
Aldols **7** proved sensitive to both strong acid and alkaline conditions. After much experimentation, suitable conditions were found for acetonide cleavage and selective elimination of protecting groups (Scheme 3). Thus, compounds **7** (R=TBS and R′=Et, *i*Pr, Ph, *p*-ClC_6H_4)[13] were treated with periodic acid hydrate in ethyl acetate[14] under carefully controlled conditions (see Experimental). The acids formed were isolated as their methyl esters and assigned structure **8** on the basis of spectroscopic findings and the subsequent synthetic manipulations.[15] Selective hydrolysis of the formyl group in **8** took place under very mild basic conditions[16] to yield the monoprotected dihydroxy esters **9**. Selective cleavage of the silyl group in **8** without deformylation proved infeasible. However, treatment of either **8**, **9** or their mixture[15] with hydrogen fluoride[16] provided dihydroxy esters **10**.[17] The formation of the *O*-formylated derivatives **8** in the oxidative cleavage of **7** with periodic acid can be explained with the mechanism in Scheme 4.

Esters **9** and **10** should be amenable to conversion, via appropriate nucleophilic substitution of hydroxyl groups, into various compounds of pharmacological interest such as, for example, β-hydroxy-α-amino acids, α-hydroxy-β-amino acids or α,β-diamino acids.[18] Furthermore, since D-erythrulose acetonides enantiomeric to **6** are also easily available,[8] the preparation of compounds antipodal to those depicted later is also feasible. Efforts in these directions are presently underway in our group.

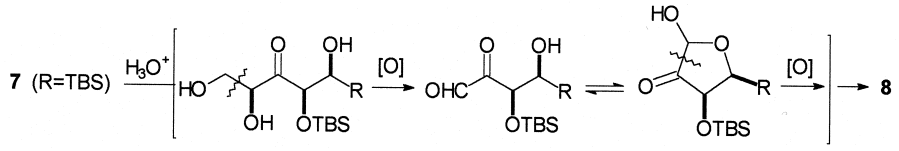
A further interesting question that has to be addressed is the mechanistic basis of the unexpected stereochemical outcome of aldol reactions with ketones **6** promoted by Chx_2BCl. Until our results, only a single case had been described in which this reagent leads to the formation of *syn* aldols,[19] *anti* aldols being formed otherwise very predominantly.[20] If the usually accepted cyclic transition state[21] in the aldol addition itself is assumed, we should conclude that a (*Z*) boron enolate was formed, in contrast to that expected for Chx_2BCl.[20] In fact, recent computational calculations by our group[22,23] support the conclusion that the observed aldol adducts are formed through the (*Z*) boron enolate participating in a chair-like transition state of the Zimmerman–Traxler type.[21] If this is the case, we must explain why enolization with Chx_2BCl gives rise here to a (*Z*) boron enolate, rather than to the expected (*E*) enolate.[24] Both theoretical and experimental work in this direction is now underway and will be reported in due course.

Experimental

NMR spectra were measured in a $CDCl_3$ solution at 25°C (Varian Unity 500 and 400 NMR spectrometers). Mass spectra were run either by the electron impact (EIMS, 70 eV), chemical ionization (CIMS, CH_4) or fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR spectra were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 22°C. Reactions that required an inert atmosphere were carried out under argon with flame-dried glassware. Commercial



Scheme 3. Reaction conditions. (a) H_5IO_6, EtOAc, room temperature, 2 h, then CH_2N_2. Yields: **8** (60–74%) and **9** (10–13%). (b) $KHCO_3$/MeOH, 0°C, 1 h. Yields: 80–85%. (c) HF-pyridine/MeCN, room temperature, 6 h. Yields: 75–85% (for the conversion **8→10**).



Scheme 4.

reagents (Aldrich or Fluka) were used as received. Hexane solutions of Chx_2BCl were generated by hydroboration of cyclohexene with monochloroborane as reported in the literature.[25] Et_2O and THF were freshly distilled under Ar from sodium-benzophenone ketyl. Dichloromethane was distilled from P_2O_5 and stored over 4 Å molecular sieves. Tertiary amines were distilled from CaH_2. Unless detailed otherwise, "work-up" means pouring the reaction mixture into brine, extracting with the indicated solvent, additional washing with 5% aq. $NaHCO_3$ (if acids had been utilized in the reaction) or with 5% aq. HCl (if bases had been utilized), then again with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and eliminating the solvent in vacuo. The obtained material was then chromatographed on a silica gel column (Süd-Chemie AG, 60-200) with the indicated eluant.

General procedure for aldol additions of erythrulose derivatives 6 (all aldol reactions were performed under an inert atmosphere). To a stirred solution of Chx_2BCl (1.8 mL of a 1 M hexane solution, 1.8 mmol) and Et_3N (278 μL, 2 mmol) in anhydrous Et_2O (6 mL) at −78°C was added erythrulose derivative **6**[8] (1 mmol) in anhydrous ether (6 mL). After 10 min, the reaction mixture was warmed to 0°C for 1 h and then recooled to −78°C. A solution of the aldehyde (5 mmol) in ether (6 mL) was added and after 10 min. at −78°C the reaction mixture was warmed to 0°C and stirred at this temperature for 5 h. Then pH 7 phosphate buffer (6 mL) and MeOH (6 mL) were added at 0°C followed by 30% aq. H_2O_2 solution (3 mL). After stirring for 1 h at room temperature, the mixture was worked up (extraction with Et_2O). Solvent removal in vacuo and column chromatography of the residue on silica gel (hexane–EtOAc 9:1 and then 4:1) afforded the aldol addition product **7** as essentially one diastereoisomer. Chemical yields: R=TES, **7a** (85%), **7b** (77%), **7c** (80%), **7d** (87%); R=TBS, **7a** (87%), **7b** (86%), **7c** (83%), **7d** (86%), **7e** (89%), **7f** (85%); R=TPS, **7b** (85%), **7c** (78%). When Et_2O was replaced by THF or CH_2Cl_2, or when Et_3N was replaced by $EtNMe_2$ or $EtNiPr_2$, yields and d.r.'s remained essentially unchanged.

(2*S*,4*R*,5*S*)-4-*O*-Triethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxyheptan-3-one, 7a (R=TES). Oil, $[\alpha]_D$ −8.9 ($CHCl_3$, *c* 6.5); IR ν_{max} cm^{-1}: 3420 (br, OH), 1728 (ketone C=O), 1634, 1485, 1335, 850; CIMS, *m/z* 333.2104 ($M+H^+$). Calc. for $C_{16}H_{33}O_5Si$, M=333.2097; ^1H NMR (400 MHz): δ 4.67 (1H, *d*, *J*=2.2 Hz, H-4), 4.64 (1H, *dd*, *J*=7.7, 5.3 Hz, H-2), 4.20 (1H, *dd*, *J*=8.8, 7.7 Hz, H-1), 4.11 (1H, *dd*, *J*=8.8, 5.3 Hz, H-1′), 3.93 (1H, *br m*, H-5), 2.25 (1H, *br d*, *J*=9 Hz, OH), 1.57 (2H, *quint*, *J*=7.2 Hz, H-6), 1.42, 1.37 (2×3H, 2×*s*, acetonide *Me*), 0.99 (3H, *t*, *J*=7.2 Hz, H-7), 0.95 (9H, *t*, *J*=8 Hz, 3×$SiCH_2Me$), 0.60 (6H, 2×*q*, *J*~8 Hz, 3×$SiCH_2Me$); ^{13}C NMR (100 MHz): δ 208.5 (C-3), 110.7 (acetonide C), 78.5 (C-2), 77.8 (C-4), 73.1 (C-5), 66.4 (C-1), 27.2 (C-6), 26.0, 24.9 (acetonide *Me*), 10.2 (C-7), 6.7 ($MeCH_2Si$), 4.7 ($MeCH_2Si$).

(2*S*,4*R*,5*S*)-4-*O*-Triethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-6-methylheptan-3-one, 7b (R=TES). Oil, $[\alpha]_D$ −15.4 ($CHCl_3$, *c* 1.1); IR ν_{max} cm^{-1}: 3440 (br, OH), 1729 (ketone C=O), 1472, 1384, 1256, 1106, 838; CIMS, *m/z* 347.2251 ($M+H^+$). Calc. for $C_{17}H_{35}O_5Si$, M=347.2253; ^1H NMR (400 MHz): δ 4.90 (1H, *d*, *J*=1.5 Hz, H-4), 4.60 (1H, *dd*, *J*=7.5, 5.3 Hz, H-2), 4.18 (1H, *dd*, *J*=8.8, 7.5 Hz, H-1), 4.12 (1H, *dd*, *J*=8.8, 5.3 Hz, H-1′), 3.63 (1H, *br d*, *J*=9 Hz, H-5), 2.20 (1H, *br s*, OH), 1.78 (1H, *dqq*, *J*=9, 7, 7 Hz, H-6), 1.41, 1.36 (2×3H, 2×*s*, acetonide *Me*), 1.03, 0.95 (2×3H, 2×*d*, *J*=7 Hz, isopropyl *Me*), 0.95 (9H, *t*, *J*=8 Hz, 3×$SiCH_2Me$), 0.60 (6H, *m*, 3×$SiCH_2Me$); ^{13}C NMR (100 MHz): δ 208.9 (C-3), 110.8 (acetonide C), 78.5 (C-2), 76.7 (C-5), 76.3 (C-4), 66.7 (C-1), 31.4 (C-6), 26.1, 24.8 (acetonide *Me*), 19.1, 19.0 (isopropyl *Me*), 6.7 ($MeCH_2Si$), 4.9 ($MeCH_2Si$).

(2*S*,4*R*,5*S*)-4-*O*-Triethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-5-phenylpentan-3-one, 7c (R=TES). Oil, $[\alpha]_D$ −17.8 ($CHCl_3$, *c* 1.5); IR ν_{max} cm^{-1}: 3420 (br, OH), 1736 (ketone C=O), 1372, 1256, 1073, 840; FABMS, *m/z* 403.1918 ($M+Na^+$). Calc. for $C_{20}H_{32}O_5SiNa$, M=403.1916; ^1H NMR (400 MHz): δ 7.40–7.20 (5H, *m*, aromatic), 5.26 (1H, *br d*, *J*=2 Hz, H-5), 4.89 (1H, *d*, *J*=2 Hz, H-4), 4.64 (1H, *dd*, *J*=7.8, 5.2 Hz, H-2), 4.22 (1H, *dd*, *J*=8.8, 7.8 Hz, H-1), 4.10 (1H, *dd*, *J*=8.8, 5.2 Hz, H-1′), 1.50, 1.41 (2×3H, 2×*s*, acetonide *Me*), 0.74 (9H, *t*, *J*=8 Hz, 3×$SiCH_2Me$), 0.35 (6H, *m*, 3×$SiCH_2Me$); ^{13}C NMR (100 MHz): δ 207.8 (C-3), 141.2, 128.1, 127.5, 125.7 (aromatic), 110.9 (acetonide C), 79.9 (C-4), 78.8 (C-2), 72.9 (C-5), 66.7 (C-1), 26.1, 24.9 (acetonide *Me*), 6.5 ($MeCH_2Si$), 4.3 ($MeCH_2Si$).

(2*S*,4*R*,5*S*)-4-*O*-Triethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-5-(*p*-chlorophenyl)pentan-3-one, 7d (R=TES). Oil, $[\alpha]_D$ −70.4 ($CHCl_3$, *c* 1.8); IR ν_{max} cm^{-1}: 3420 (br, OH), 1734 (ketone C=O), 1372, 1286, 1158, 840; FABMS, *m/z* 437.1543 ($M+Na^+$). Calc. for $C_{20}H_{31}O_5{}^{35}ClSiNa$, M=437.1527; ^1H NMR (400 MHz): δ 7.35–7.25 (4H, *m*, aromatic), 5.22 (1H, *br s*, H-5), 4.84 (1H, *d*, *J*=2 Hz, H-4), 4.64 (1H, *dd*, *J*=7.7, 5.2 Hz, H-2), 4.23 (1H, *dd*, *J*=8.8, 7.7 Hz, H-1), 4.10 (1H, *dd*, *J*=8.8, 5.2 Hz, H-1′), 1.49, 1.40 (2×3H, 2×*s*, acetonide *Me*), 0.75 (9H, *t*, *J*=8 Hz, 3×$SiCH_2Me$), 0.35 (6H, *m*, 3×$SiCH_2Me$); ^{13}C NMR (100 MHz): δ 207.5 (C-3), 139.9, 133.2, 128.3, 127.2 (aromatic), 111.0 (acetonide C), 79.6 (C-4), 78.7 (C-2), 72.3 (C-5), 66.7 (C-1), 26.1, 24.8 (acetonide *Me*), 6.4 ($MeCH_2Si$), 4.4 ($MeCH_2Si$).

(2*S*,4*R*,5*S*)-4-*O*-*t*-Butyldimethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxyheptan-3-one, 7a (R=TBS). Oil, $[\alpha]_D$ −47.4 ($CHCl_3$, *c* 4.9); IR ν_{max} cm^{-1}: 3460 (br, OH), 1724 (ketone C=O), 1454, 1385, 1252, 1152, 1054, 837; FABMS, *m/z* 333.2106 ($M+H^+$). Calc. for $C_{16}H_{33}O_5Si$, M=333.2097; ^1H NMR (400 MHz): δ 4.66 (1H, *d*, *J*=2 Hz, H-4), 4.62 (1H, *dd*, *J*=7.5, 5.3 Hz, H-2), 4.16 (1H, *dd*, *J*=8.8, 7.5 Hz, H-1), 4.10 (1H, *dd*, *J*=8.8, 5.3 Hz, H-1′), 3.95 (1H, *m*, H-5), 2.10 (1H, *br d*, *J*=10.5 Hz, OH), 1.55 (2H, *m*, H-6), 1.40, 1.35 (2×3H, 2×*s*, acetonide *Me*), 0.97 (3H, *t*, *J*=7.5 Hz, H-7), 0.89 (9H, *s*, $SiCMe_3$), 0.06, −0.02 (2×3H, 2×*s*, $SiMe_2$); ^{13}C NMR (100 MHz): δ 208.5 (C-3), 110.7 (acetonide C), 78.5 (C-2), 77.9 (C-4), 73.1 (C-5), 66.5 (C-1), 27.4 (C-6), 26.0, 24.9 (acetonide *Me*), 25.7 ($SiCMe_3$), 18.4 ($SiCMe_3$), 10.3 (C-7), −4.6, −5.4 ($SiMe_2$).

(2*S*,4*R*,5*S*)-4-*O*-*t*-Butyldimethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-6-methylheptan-3-one, 7b (R=TBS). Oil, $[\alpha]_D$ −16.5 ($CHCl_3$, *c* 5.5); IR ν_{max} cm^{-1}: 3440 (br, OH),

1732 (ketone C═O), 1472, 1384, 1256, 1106, 838; FABMS, *m/z* 369.2068 $(M+Na)^+$. Calc. for $C_{17}H_{34}O_5SiNa$, M=369.2073; ^1H NMR (400 MHz): δ 4.91 (1H, *d*, *J*=1.5 Hz, H-4), 4.59 (1H, *dd*, *J*=7.4, 5.2 Hz, H-2), 4.18 (1H, *dd*, *J*=8.8, 7.4 Hz, H-1), 4.12 (1H, *dd*, *J*=8.8, 5.2 Hz, H-1′), 3.63 (1H, *br t*, *J*=9.5 Hz, H-5), 2.10 (1H, *br d*, *J*=9.5 Hz, OH), 1.78 (1H, *dqq*, *J*=9, 7, 7 Hz, H-6), 1.41, 1.36 (2×3H, 2×*s*, acetonide *Me*), 1.03, 0.94 (2×3H, 2×*d*, *J*=7 Hz, isopropyl *Me*), 0.90 (9H, *s*, SiC*Me*$_3$), 0.08, −0.01 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (100 MHz): δ 208.9 (C-3), 110.8 (acetonide C), 78.5 (C-2), 76.7 (C-5), 76.3 (C-4), 66.7 (C-1), 31.4 (C-6), 26.1, 24.9 (acetonide *Me*), 25.8 (SiC*Me*$_3$), 19.2, 19.0 (isopropyl *Me*), 18.4 (Si*C*Me$_3$), −4.3, −5.4 (Si*Me*$_2$).

(2*S*,4*R*,5*S*)-4-*O*-*t*-Butyldimethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-5-phenylpentan-3-one, 7c (R=TBS). Oil, $[\alpha]_D$ −9.6 ($CHCl_3$, *c* 1.2); IR ν_{max} cm^{-1}: 3460 (br, OH), 1731 (ketone C═O), 1450, 1250, 1080, 940; FABMS, *m/z* 403.1928 $(M+Na)^+$. Calc. for $C_{20}H_{32}O_5SiNa$, M=403.1916; ^1H NMR (400 MHz): δ 7.35–7.25 (5H, *m*, aromatic), 5.31 (1H, *br d*, *J*=2 Hz, H-5), 4.88 (1H, *d*, *J*=2 Hz, H-4), 4.68 (1H, *dd*, *J*=7.7, 5.2 Hz, H-2), 4.23 (1H, *dd*, *J*=8.8, 7.7 Hz, H-1), 4.12 (1H, *dd*, *J*=8.8, 5.2 Hz, H-1′), 1.51, 1.42 (2×3H, 2×*s*, acetonide *Me*), 0.72 (9H, *s*, SiC*Me*$_3$), −0.17, −0.40 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (100 MHz): δ 207.8 (C-3), 141.2, 128.1, 127.5, 125.7 (aromatic), 111.0 (acetonide C), 80.3 (C-4), 78.7 (C-2), 72.7 (C-5), 66.7 (C-1), 26.2, 24.9 (acetonide *Me*), 25.5 (SiC*Me*$_3$), 18.2 (Si*C*Me$_3$), −5.3, −6.0 (Si*Me*$_2$).

(2*S*,4*R*,5*S*)-4-*O*-*t*-Butyldimethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-5-(*p*-chlorophenyl)pentan-3-one, 7d (R=TBS). Colourless needles, mp 110–112°C (from hexane–CH_2Cl_2), $[\alpha]_D$ −41.4 ($CHCl_3$, *c* 0.8); IR ν_{max} cm^{-1}: 3420 (br, OH), 1734 (ketone C═O), 1383, 1257, 1090, 838; FABMS, *m/z* 437.1527 $(M+Na)^+$. Calc. for $C_{20}H_{31}O_5{}^{35}ClSiNa$, M=437.1527; ^1H NMR (400 MHz): δ 7.35–7.25 (4H, *m*, aromatic), 5.27 (1H, *br d*, *J*=2 Hz, H-5), 4.83 (1H, *d*, *J*=2 Hz, H-4), 4.67 (1H, *dd*, *J*=7.7, 5.2 Hz, H-2), 4.24 (1H, *dd*, *J*=8.8, 7.7 Hz, H-1), 4.13 (1H, *dd*, *J*=8.8, 5.2 Hz, H-1′), 1.50, 1.42 (2×3H, 2×*s*, acetonide *Me*), 0.74 (9H, *s*, SiC*Me*$_3$), −0.14, −0.38 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (100 MHz): δ 207.5 (C-3), 139.9, 133.2, 128.3, 127.1 (aromatic), 111.1 (acetonide C), 80.0 (C-4), 78.7 (C-2), 72.2 (C-5), 66.7 (C-1), 26.2, 24.9 (acetonide *Me*), 25.5 (SiC*Me*$_3$), 18.2 (Si*C*Me$_3$), −5.2, −5.9 (Si*Me*$_2$). Elemental analysis: Found, C, 57.77%; H, 7.70%. Calc. for $C_{20}H_{31}O_5ClSi$: C, 57.88%; H, 7.53%.

(2*S*,4*R*,5*S*)-4-*O*-*t*-Butyldimethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-5-(*p*-nitrophenyl)pentan-3-one, 7e (R=TBS). Yellowish needles, mp 124–125°C (from hexane–CH_2Cl_2), $[\alpha]_D$ −10.3 ($CHCl_3$, *c* 3.5); IR ν_{max} cm^{-1}: 3420 (br, OH), 1734 (ketone C═O), 1383, 1258, 838; FABMS, *m/z* 448.1775 $(M+Na^+)$ Calc. for $C_{20}H_{31}NO_7SiNa$, M=448.1767; ^1H NMR (400 MHz): δ 8.24 (2H, *d*, *J*=8.8 Hz, aromatic), 7.56 (2H, *d*, *J*=8.8 Hz, aromatic), 5.41 (1H, *br d*, *J*=9.5 Hz, H-5), 4.92 (1H, *d*, *J*=1.5 Hz, H-4), 4.72 (1H, *dd*, *J*=7.7, 5 Hz, H-2), 4.28 (1H, *dd*, *J*=8.8, 7.7 Hz, H-1), 4.17 (1H, *dd*, *J*=8.8, 5 Hz, H-1′), 3.20 (1H, *d*, *J*=9.5 Hz, OH), 1.54, 1.45 (2×3H, 2×*s*, acetonide *Me*), 0.72 (9H, *s*, SiC*Me*$_3$), −0.11, −0.40 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (100 MHz): δ 207.0 (C-3), 149.2, 147.3, 126.6, 123.5 (aromatic), 111.3 (acetonide C), 79.7 (C-4), 78.7 (C-2), 72.1 (C-5), 66.8 (C-1), 26.3, 24.9 (acetonide *Me*), 25.4 (SiC*Me*$_3$), 18.2 (Si*C*Me$_3$), −5.1, −5.9 (Si*Me*$_2$). Elemental analysis: Found, C, 56.66%; H, 7.50%; N, 3.37. Calc. for $C_{20}H_{31}NO_7Si$: C, 56.45%; H, 7.34%; N, 3.45%.

(2*S*,4*R*,5*S*)-4-*O*-*t*-Butyldimethylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-6-methylhept-6-en-3-one, 7f (R=TBS). Oil, $[\alpha]_D$ −15.4 ($CHCl_3$, *c* 1.5); IR ν_{max} cm^{-1}: 3450 (br, OH), 1730 (ketone C═O), 1495, 1345, 1267, 790; EIMS, *m/z* (% rel. int.): 329.1777 ($M-Me^+$, 2), 274 (23), 75 (100). Calc. for $C_{16}H_{29}O_5Si$, M=329.1784; ^1H NMR (400 MHz): δ 5.03 (1H, *br s*, H-7), 4.97 (1H, *q*, *J*=1.5 Hz, H-7′), 4.84 (1H, *d*, *J*=2 Hz, H-4), 4.64 (1H, *dd*, *J*=7.7, 5.2 Hz, H-2), 4.50 (1H, *br s*, H-5), 4.20 (1H, *dd*, *J*=8.8, 7.7 Hz, H-1), 4.10 (1H, *dd*, *J*=8.8, 5.2 Hz, H-1′), 1.78 (3H, *br s*, *Me*-C6), 1.44, 1.37 (2×3H, 2×*s*, acetonide *Me*), 0.86 (9H, *s*, SiC*Me*$_3$), 0.04, −0.05 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (100 MHz): δ 208.2 (C-3), 143.6 (C-6), 111.9 (C-7), 110.9 (acetonide C), 78.6 (C-2), 76.6 (C-4), 73.8 (C-5), 66.7 (C-1), 26.1, 24.9 (acetonide *Me*), 25.7 (SiC*Me*$_3$), 19.2 (*Me*-C6), 18.4 (Si*C*Me$_3$), −4.7, −5.5 (Si*Me*$_2$).

(2*S*,4*R*,5*S*)-4-*O*-*t*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-6-methylheptan-3-one, 7b (R=TBDPS). Oil, $[\alpha]_D$ −62.7 ($CHCl_3$, *c* 1.4); IR ν_{max} cm^{-1}: 3470 (br, OH), 1752 (ketone C═O), 1476, 1364, 1260, 1100; FABMS, *m/z* 493.2392 $(M+Na^+)$. Calc. for $C_{27}H_{38}O_5SiNa$, M=493.2386; ^1H NMR (400 MHz): δ 7.70–7.60 (4H, *m*, aromatic), 7.45–7.30 (6H, *m*, aromatic), 4.96 (1H, *br s*, H-4), 4.38 (1H, *dd*, *J*=7.7, 6.3 Hz, H-2), 3.88 (1H, *dd*, *J*=8.8, 7.7 Hz, H-1), 3.65 (1H, *br t*, *J*∼10.5 Hz, H-5), 3.10 (1H, *dd*, *J*=8.8, 6.3 Hz, H-1′), 2.20 (1H, *d*, *J*=11 Hz, OH), 1.92 (1H, *dqq*, *J*=10.5, 7, 7 Hz, H-6), 1.23, 1.06 (2×3H, 2×*s*, acetonide *Me*), 1.10 (9H, *s*, SiC*Me*$_3$), 1.07, 0.77 (2×3H, 2×*d*, *J*=7 Hz, isopropyl *Me*); ^{13}C NMR (100 MHz): δ 207.7 (C-3), 136.1, 136.0, 133.0, 129.8, 129.8, 127.7, 127.4 (aromatic), 110.7 (acetonide C), 78.6 (C-2), 76.7 (C-4, C-5), 66.3 (C-1), 31.6 (C-6), 27.2 (SiC*Me*$_3$), 25.7, 25.0 (acetonide *Me*), 19.8 (Si*C*Me$_3$), 19.4, 18.9 (isopropyl *Me*).

(2*S*,4*R*,5*S*)-4-*O*-*t*-Butyldiphenylsilyl-1,2-*O*-isopropylidene-1,2,4,5-tetrahydroxy-5-phenylpentan-3-one, 7c (R=TBDPS). Oil, $[\alpha]_D$ −69.6 ($CHCl_3$, *c* 0.8); IR ν_{max} cm^{-1}: 3460 (br, OH), 1766 (ketone C═O), 1324, 1240, 1050, 938, 840; FABMS, *m/z* 528.2316 $(M+H+Na)^+$. Calc. for $C_{30}H_{37}O_5SiNa$, M=528.2308; ^1H NMR (400 MHz): δ 7.60–7.00 (15H, *m*, aromatic), 5.38 (1H, *br s*, H-5), 5.04 (1H, *d*, *J*=1.5 Hz, H-4), 4.42 (1H, *dd*, *J*=7.7, 6.5 Hz, H-2), 3.84 (1H, *dd*, *J*=8.8, 7.7 Hz, H-1), 3.20 (1H, *br s*, OH), 2.92 (1H, *dd*, *J*=8.8, 6.5 Hz, H-1′), 1.31, 1.22 (2×3H, 2×*s*, acetonide *Me*), 1.00 (9H, *s*, SiC*Me*$_3$); ^{13}C NMR (100 MHz): δ 206.6 (C-3), 141.4, 136.3, 135.7, 132.7, 132.5, 129.9, 129.6, 128.4, 127.6, 127.5, 127.4, 125.8 (aromatic), 110.9 (acetonide C), 80.3 (C-4), 78.7 (C-2), 72.3 (C-5), 66.2 (C-1), 26.9 (SiC*Me*$_3$), 25.9, 25.0 (acetonide *Me*), 19.4 (Si*C*Me$_3$).

Periodic acid cleavage of aldols 7. The aldol (1 mmol) was dissolved in EtOAc (10 mL) and treated with H_5IO_6 (800 mg, ca. 3.5 mmol). After stirring at room temperature

until consumption of **7** (ca. 2 h, TLC monitoring), solid sodium thiosulfate (320 mg, ca. 2 mmol) was added. The reaction mixture was stirred for 5 min, filtered and evaporated in vacuo, and the oily residue was treated with ethereal diazomethane. Column chromatography on silica gel (hexane–Et_2O 19:1, then 9:1) afforded **8** and **9**. Chemical yields: **8a** (60%), **8b** (66%), **8c** (74%), **8d** (71%); **9a** (10%), **9b** (11%), **9c** (13%), **9d** (12%).

Methyl (2*R*,3*S*)-2-*O*-*t*-butyldimethylsilyl-3-*O*-formyl-2,3-dihydroxypentanoate, 8a. Oil, $[\alpha]_D$ −15.2 ($CHCl_3$, *c* 1.1); IR ν_{max} cm^{-1}: 1760, 1729 (ester C=O), 1255, 1168, 1085, 838, 780; CIMS, *m/z* 291.1619 ($M+H^+$). Calc. for $C_{13}H_{27}O_5Si$, M=291.1627; ^1H NMR (500 MHz): δ 8.06 (1H, *s*, OCHO), 5.10 (1H, *dt*, *J*=4.5, 4 Hz, H-3), 4.28 (1H, *d*, *J*=4 Hz, H-2), 3.70 (3H, *s*, OMe), 1.67 (2H, *m*, H-4), 0.92 (3H, *t*, *J*=7.5 Hz, H-5), 0.89 (9H, *s*, SiC*Me*$_3$), 0.08, 0.04 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 171.4 (C-1), 160.6 (*C*HO), 76.1 (C-2), 73.0 (C-3), 52.1 (OMe), 25.7 (SiC*Me*$_3$), 23.2 (C-4), 18.3 (Si*C*Me$_3$), 9.9 (C-5), −4.9, −5.5 (Si*Me*$_2$).

Methyl (2*R*,3*S*)-2-*O*-*t*-butyldimethylsilyl-3-*O*-formyl-2,3-dihydroxy-4-methylpentanoate, 8b. Oil, $[\alpha]_D$ −11.3 ($CHCl_3$, *c* 1.3); IR ν_{max} cm^{-1}: 1759, 1729 (ester C=O), 1467, 1257, 1164, 1110, 836, 780; CIMS, *m/z* 305.1789 ($M+H^+$). Calc. for $C_{14}H_{29}O_5Si$, M=305.1784; ^1H NMR (500 MHz): δ 8.07 (1H, *s*, OCHO), 4.97 (1H, *dd*, *J*=7.3, 4.2 Hz, H-3), 4.36 (1H, *d*, *J*=4.2 Hz, H-2), 3.67 (3H, *s*, OMe), 2.00 (1H, *dqq*, *J*=7.3, 7. 7 Hz, H-4), 0.94, 0.90 (2×3H, 2×*d*, *J*=7 Hz, H-5 and *Me*-C4), 0.87 (9H, *s*, SiC*Me*$_3$), 0.07, 0.03 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 171.6 (C-1), 160.6 (*C*HO), 79.1 (C-3), 72.2 (C-2), 52.0 (OMe), 28.1 (C-4), 25.6 (SiC*Me*$_3$), 19.1, 17.9 (C-5 and *Me*-C4), 18.2 (Si*C*Me$_3$), −4.8, −5.4 (Si*Me*$_2$).

Methyl (2*R*,3*S*)-2-*O*-*t*-butyldimethylsilyl-3-*O*-formyl-2,3-dihydroxy-3-phenylpropionate, 8c. Oil, $[\alpha]_D$ +40.9 ($CHCl_3$, *c* 1.7); IR ν_{max} cm^{-1}: 1759, 1734 (ester C=O), 1257, 1156, 1021, 837, 780; CIMS, *m/z* 293.1567 ($M+H^+-HCOOH$). Calc. for $C_{16}H_{25}O_3Si$, M=293.1572; ^1H NMR (500 MHz): δ 8.14 (1H, *s*, OCHO), 7.40–7.25 (5H, *m*, aromatic), 6.17 (1H, *d*, *J*=4.3 Hz, H-3), 4.42 (1H, *d*, *J*=4.3 Hz, H-2), 3.65 (3H, *s*, OMe), 0.79 (9H, *s*, SiC*Me*$_3$), −0.13, −0.17 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 170.7 (C-1), 159.8 (*C*HO), 135.7, 128.6, 128.4, 127.1 (aromatic), 76.5 (C-3), 75.6 (C-2), 52.2 (OMe), 25.5 (SiC*Me*$_3$), 18.3 (Si*C*Me$_3$), −5.6, −5.7 (Si*Me*$_2$).

Methyl (2*R*,3*S*)-2-*O*-*t*-butyldimethylsilyl-3-*O*-formyl-2,3-dihydroxy-3-(*p*-chlorophenyl)propionate, 8d. Oil, $[\alpha]_D$ +44.8 ($CHCl_3$, *c* 1.1); IR ν_{max} cm^{-1}: 1760, 1734 (ester C=O), 1494, 1257, 1157, 1092, 1015, 837, 780; CIMS, *m/z*327.1189 ($M+H^+-HCOOH$). Calc. for $C_{16}H_{24}O_3Si^{35}Cl$, M=327.1183; ^1H NMR (500 MHz): δ 8.09 (1H, *s*, OCHO), 7.35–7.25 (4H, *m*, aromatic), 6.12 (1H, *d*, *J*=4.4 Hz, H-3), 4.38 (1H, *d*, *J*=4.4 Hz, H-2), 3.64 (3H, *s*, OMe), 0.78 (9H, *s*, SiC*Me*$_3$), −0.11, −0.18 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 170.4 (C-1), 159.6 (*C*HO), 134.5, 134.3, 128.6 (aromatic), 75.6 (C-2), 75.2 (C-3), 52.2 (OMe), 25.4 (SiC*Me*$_3$), 18.2 (Si*C*Me$_3$), −5.6, −5.7 (Si*Me*$_2$).

Alkaline deformylation of esters 8. The ester (1 mmol) was dissolved in dry MeOH (5 mL), cooled to 0°C and treated with solid $KHCO_3$ (110 mg, ca. 1.1 mmol). After stirring at 0°C for ca. 1 h (TLC monitoring), the mixture was worked up and chromatographed on silica gel (hexane–EtOAc 9:1) to yield **9**. Chemical yields: **9a** (82%), **9b** (80%), **9c** (85%), **9d** (85%).

Methyl (2*R*,3*S*)-2-*O*-*t*-butyldimethylsilyl-2,3-dihydroxypentanoate, 9a. Oil, $[\alpha]_D$ +25.2 ($CHCl_3$, *c* 0.9); IR ν_{max} cm^{-1}: 3410 (br, OH), 1759, 1730sh (ester C=O), 1462, 1256, 1151, 838, 780; CIMS, *m/z* 263.1685 ($M+H^+$). Calc. for $C_{12}H_{27}O_4Si$, M=263.1678; ^1H NMR (500 MHz): δ 4.09 (1H, *d*, *J*=3 Hz, H-2), 3.70 (3H, *s*, OMe), 3.68 (1H, *br m*, H-3), 2.20 (1H, *br s*, OH), 1.48 (2H, *m*, H-4), 0.94 (3H, *t*, *J*=7.5 Hz, H-5), 0.88 (9H, *s*, SiC*Me*$_3$), 0.07, 0.02 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 172.7 (C-1), 74.8, 74.5 (C-2, C-3), 51.9 (OMe), 26.7 (C-4), 25.7 (SiC*Me*$_3$), 18.3 (Si*C*Me$_3$), 10.2 (C-5), −4.9, −5.5 (Si*Me*$_2$).

Methyl (2*R*,3*S*)-2-*O*-*t*-butyldimethylsilyl-2,3-dihydroxy-4-methylpentanoate, 9b. Oil, $[\alpha]_D$ +31.1 ($CHCl_3$, *c* 1.5); IR ν_{max} cm^{-1}: 3420 (br, OH), 1760, 1730sh (ester C=O), 1470, 1390, 1364, 1256, 1150, 1109, 1007, 983, 838, 780; CIMS, *m/z* 277.1833 ($M+H^+$). Calc. for $C_{13}H_{29}O_4Si$, M=277.1835; ^1H NMR (500 MHz): δ 4.30 (1H, *d*, *J*=2.5 Hz, H-2), 3.72 (3H, *s*, OMe), 3.40 (1H, *br d*, *J*=2.5 Hz, H-3), 2.20 (1H, *br s*, OH), 1.72 (1H, *m*, H-4), 1.00, 0.91 (2×3H, 2×*d*, *J*=7 Hz, H-5 and *Me*-C4), 0.90 (9H, *s*, SiC*Me*$_3$), 0.10, 0.04 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 173.0 (C-1), 78.6 (C-3), 72.7 (C-2), 51.9 (OMe), 30.7 (C-4), 25.7 (SiC*Me*$_3$), 19.2, 18.6 (C-5 and *Me*-C4), 18.3 (Si*C*Me$_3$), −4.7, −5.4 (Si*Me*$_2$).

Methyl (2*R*,3*S*)-2-*O*-*t*-butyldimethylsilyl-2,3-dihydroxy-3-phenylpropionate, 9c. Oil, $[\alpha]_D$ +27.5 ($CHCl_3$, *c* 1.6); IR ν_{max} cm^{-1}: 3390 (br, OH), 1757, 1734sh (ester C=O), 1452, 1437, 1255, 1143, 1057, 837, 780; CIMS, *m/z* 293.1568 ($M+H^+-H_2O$). Calc. for $C_{16}H_{25}O_3Si$, M=293.1572; ^1H NMR (500 MHz): δ 7.35–7.25 (5H, *m*, aromatic), 5.01 (1H, *br d*, *J*~3 Hz, H-3), 4.30 (1H, *d*, *J*=3.4 Hz, H-2), 3.72 (3H, *s*, OMe), 3.00 (1H, *s*, OH), 0.78 (9H, *s*, SiC*Me*$_3$), −0.10, −0.25 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 172.0 (C-1), 140.4, 128.2, 127.7, 126.1 (aromatic), 76.9 (C-2), 75.1 (C-3), 52.1 (OMe), 25.5 (SiC*Me*$_3$), 18.2 (Si*C*Me$_3$), −5.5, −5.8 (Si*Me*$_2$).

Methyl (2*R*,3*S*)-2-*O*-*t*-butyldimethylsilyl-2,3-dihydroxy-3-(*p*-chlorophenyl)propionate, 9d. Oil, $[\alpha]_D$ +25.1 ($CHCl_3$, *c* 3.6); IR ν_{max} cm^{-1}: 3470 (br, OH), 1760, 1735sh (ester C=O), 1493, 1463, 1437, 1409, 1362, 1257, 1145, 1092, 1065, 1015, 953, 835, 781; CIMS, *m/z* 327.1186 ($M+H^+-H_2O$). Calc. for $C_{16}H_{24}O_3Si^{35}Cl$, M=327.1183; ^1H NMR (500 MHz): δ 7.35–7.25 (4H, *m*, aromatic), 4.96 (1H, *dd*, *J*=7, 3.3 Hz, H-3), 4.25 (1H, *d*, *J*=3.3 Hz, H-2), 3.70 (3H, *s*, OMe), 3.10 (1H, *d*, *J*=7 Hz, OH), 0.77 (9H, *s*, SiC*Me*$_3$), −0.08, −0.23 (2×3H, 2×*s*, Si*Me*$_2$); ^{13}C NMR (125 MHz): δ 171.7 (C-1), 138.9, 133.5, 128.3, 127.5 (aromatic), 76.7 (C-2), 74.5 (C-3), 52.1 (OMe), 25.5 (SiC*Me*$_3$), 18.2 (Si*C*Me$_3$), −5.4, −5.7 (Si*Me*$_2$).

Deformylation/desilylation of 8 or desilylation of 9. Either ester or their mixture[15] (1 mmol) was dissolved in

acetonitrile (10 mL) and treated with 48% aq. HF (0.65 mL, 18 mmol). The reaction mixture was stirred at room temperature for 6 h, poured onto 5% aq. $NaHCO_3$ and worked up. Column chromatography on silica gel (hexane–EtOAc 1:1→EtOAc) provided dihydroxy esters **10**. Chemical yields for the direct conversion of **8** into **10**: **10a** (75%), **10b** (78%), **10c** (85%), **10d** (81%).

Methyl (2*R*,3*S*)-2,3-dihydroxypentanoate, 10a. Oil, $[\alpha]_D$ −7.5 ($CHCl_3$, *c* 1.1); IR ν_{max} cm^{-1}: 3420 (br, OH), 1735 (ester C=O), 1639, 1453, 1377, 1260, 1095, 800; CIMS, *m/z* 149.0812 ($M+H^+$). Calc. for $C_6H_{13}O_4$, M=149.0813; ^1H NMR (500 MHz): δ 4.12 (1H, *br d*, *J*=2 Hz, H-2), 3.81 (3H, *s*, OMe), 3.12 (1H, *m*, H-3), 2.10 (1H, *br s*, OH), 1.63 (2H, *quint*, *J*=7.4 Hz, H-4), 0.98 (3H, *t*, *J*=7.4 Hz, H-5); ^{13}C NMR (125 MHz): δ 174.2 (C-1), 74.0, 72.7 (C-2, C-3), 52.9 (OMe), 26.8 (C-4), 10.2 (C-5).

Methyl (2*R*,3*S*)-2,3-dihydroxy-4-methylpentanoate, 10b. Oil, $[\alpha]_D$ −6.9 ($CHCl_3$, *c* 0.5); IR ν_{max} cm^{-1}: 3380 (br, OH), 1739 (ester C=O), 1441, 1272, 1222, 1141, 1094, 1048, 798; CIMS, *m/z* 163.0972 ($M+H^+$). Calc. for $C_7H_{15}O_4$, M=163.0970; ^1H NMR (500 MHz): δ 4.29 (1H, *d*, *J*=1.5 Hz, H-2), 3.82 (3H, *s*, OMe), 3.49 (1H, *dd*, *J*=8.5, 1.5 Hz, H-3), 1.87 (1H, *m*, H-4), 1.03, 0.97 (2×3H, 2×*d*, *J*=7 Hz, H-5 and *Me*-C4); ^{13}C NMR (125 MHz): δ 174.6 (C-1), 77.8 (C-3), 71.2 (C-2), 52.9 (OMe), 31.2 (C-4), 19.1, 19.0 (C-5 and *Me*-C4).

Methyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate, 10c. Colourless solid, mp 85–87°C (from hexane–CH_2Cl_2), lit.[17] mp 84–86°C; $[\alpha]_D$ +13.3 ($CHCl_3$, *c* 0.7), +8.2 (EtOH, *c* 1.2), lit.[17] $[\alpha]_D$ +3.4 (EtOH, *c* 1.19); IR ν_{max} cm^{-1}: 3390 (br, OH), 1736 (ester C=O), 1638, 1452, 1440, 1274, 1222, 1117, 1082, 1053, 1028; ^1H NMR (500 MHz): δ 7.40 – 7.25 (5H, *m*, aromatic), 4.99 (1H, *d*, *J*=3 Hz, H-3), 4.34 (1H, *d*, *J*=3 Hz, H-2), 3.78 (3H, *s*, OMe), 3.30 (1H, *br s*, OH), 3.00 (1H, *br s*, OH); ^{13}C NMR (125 MHz): δ 173.2 (C-1), 139.9, 128.5, 128.0, 126.2 (aromatic), 74.8, 74.4 (C-2, C-3), 52.8 (OMe).

Methyl (2*R*,3*S*)-2,3-dihydroxy-3-(*p*-chlorophenyl)propionate, 10d: mp 120–122°C (from hexane–CH_2Cl_2), $[\alpha]_D$ +6.3 ($CHCl_3$, *c* 1.4); IR ν_{max} cm^{-1}: 3460 (br, OH), 1740 (ester C=O), 1492, 1440, 1400, 1337, 1225, 1105, 1054, 1014, 934, 780; EIMS, *m/z* (% rel. int.): 230.0339 (M^+, 1), 90 (100). Calc. for $C_{10}H_{11}O_4{}^{35}Cl$, M=230.0345; ^1H NMR (500 MHz): δ 7.35–7.25 (4H, *m*, aromatic), 4.94 (1H, *d*, *J*=3 Hz, H-3), 4.28 (1H, *d*, *J*=3 Hz, H-2), 3.75 (3H, *s*, OMe), 3.30 (1H, *br s*, OH); ^{13}C NMR (125 MHz): δ 173.0 (C-1), 138.4, 133.8, 128.5, 127.7 (aromatic), 74.7 (C-3), 73.8 (C-2), 52.9 (OMe). Elemental analysis: Found, C, 52.22%; H, 4.64%. Calc. for $C_{10}H_{11}O_4Cl$: C, 52.08%; H, 4.81%.

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References

1. (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982,** *13*, 1–115. (b) Mukaiyama, T. *Org. React.* **1982,** *28*, 203–331. (c) Evans, D. A. In *Asymmetric Synthesis;* Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 1–110. (d) Heathcock, C. H. In Ref. 1c, pp 111–212. (e) Heathcock, C. H. *Aldrichimica Acta* **1990,** *23*, 99–111. (f) *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press: Oxford, 1993; Vol. 2. (g) Mekelburger, H. B.; Wilcox, C. S. In Ref. 1f, pp 99–131. (h) Heathcock, C.H. In Ref. 1f, pp 133–179 and 181–238. (i) Kim, B. M.; Williams, S. F.; Masamune, S. In Ref. 1f, pp 239–275. (j) Rathke, M. W.; Weipert, P. In Ref. 1f, pp 277–299. (k) Paterson, I. In Ref. 1f, pp 301–319. (l) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994,** *1*, 317–338. (m) Braun, M. In *Houben–Weyl's Methods of Organic Chemistry, Stereoselective Synthesis;* Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. 3, pp 1603–1666, 1713–1735.

2. (a) *Recent Progress in the Chemical Synthesis of Antibiotics;* Lukacs, G., Ohno. M., Eds.; Springer: Berlin, 1990. (b) Tatsuta, K. In Ref. 2a, pp 1–38. (c) Blizzard, T.; Fisher, M.; Mrozik, H.; Shih, T. In Ref. 2a, pp 65–102. (d) Isobe, M. In Ref. 2a, pp 103–134. (e) Beau, J.-M. In Ref. 2a, pp 135–182. (f) Yonemitsu, O.; Horita, K. in Ref. 2a, pp 447–466. (g) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995,** *95*, 2041–2114.

3. Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Castillo, E.; Murga, J. *J. Org. Chem.* **1998**, *63*, 698–707.

4. (a) Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985,** *50*, 3247–3251. (b) Gray, B. D.; White, J. D. *J. Chem. Soc., Chem. Commun.* **1985,** 20–21. (c) Sugano, Y.; Naruto, S. *Chem. Pharm. Bull.* **1989,** *37*, 840–842. (d) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992,** *57*, 1961–1963. (e) Annunziata, R.; Cinquini, M.; Cozzi, F.; Borgia, A. L. *J. Org. Chem.* **1992,** *57*, 6339–6342. (f) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1993,** *58*, 5301–5303. (g) Enders, D. In *Stereoselective Synthesis;* Ottow, E., Schöllkopf, K., Schulz, B.-G., Eds.; Springer: Berlin, 1993; pp 63–90. (h) Boons, G.-J.; Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron* **1994,** *50*, 7157–7176. (i) Mukaiyama, T. *Aldrichimica Acta* **1996,** *29*, 59–76. (j) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998,** *120*, 431–432.

5. For a Mukaiyama-type aldol reaction on a ketone structurally related to **1**, see: Loh, T.-P.; Chua, G.-L.; Vittal, J.-J.; Wong, M.-W. *Chem. Commun.* **1998,** 861–862.

6. For a conceptually related synthon based on a dihydroxyacetone derivative, see: Enders, D.; Jegelka, U. *Tetrahedron Lett.* **1993,** 2453–2456. For a recent review on chiral homoenolate equivalents, see: Ahlbrecht, H.; Beyer, U. *Synthesis* **1999,** 365–390.

7. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281.

8. For the preparation of variously protected D- and L-erythrulose derivatives using chiral precursors other than erythrulose itself, see: Marco, J. A.; Carda, M.; González, F.; Rodríguez, S.; Murga, J. *Liebigs Ann. Chem.* **1996,** 1801–1810. For an improved preparation of silylated L-erythrulose acetonides **6** (R=TES, TBS, TPS) from L-erythrulose hydrate, see: Carda, M.; Rodríguez, S.; Murga, J.; Falomir, E.; Marco, J. A.; Röper, H. *Synth. Commun.* **1999,** *29*, 2601–2610.

9. The following enolization systems were tried without success

(either decomposition or recovery of starting material was observed): (a) $Sn(OTf)_2$/iPr_2NEt: Mukaiyama, T. *Aldrichimica Acta* **1996,** *29*, 59–76. (b) $TiCl_4$/iPr_2NEt: Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990,** *112*, 866–868. (c) $SnCl_4$/iPr_2NEt: Rossi, T.; Marchioro, C.; Paio, A.; Thomas, R. J.; Zarantonello, P. *J. Org. Chem.* **1997,** *62*, 1653–1661. (d) LDA or LDA/LiCl: Palomo, C.; González, A.; García, J. M.; Landa, C.; Oiarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem., Int. Ed. Engl.* **1998,** *37*, 180–182, and references cited therein. (e) n-Bu_2BOTf/tertiary amine: Mukaiyama, T.; Inoue, T. *Bull. Chem. Soc. Jpn.* **1980,** *53*, 174–178. (f) *n*-$BuBCl_2$/tertiary amine: Ramachandran, P. V.; Xu, W.-C.; Brown, H. C. *Tetrahedron Lett.* **1997,** 769–772.

10. Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **58,** 147–153. For a general review on boron aldol additions, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997,** *51*, 1–200.

11. A preliminary account of the part of the work described here has already appeared: Marco, J. A.; Carda, M.; Falomir, E.; Palomo, C.; Oiarbide, M.; Ortiz, J. A.; Linden, A. *Tetrahedron Lett.* **1999,** 1065–1068. For the influence of the protecting groups on the stereoselectivity, see: Carda, M.; Falomir, E.; Murga, J.; Castillo, E.; González, F.; Marco, J. A. *Tetrahedron Lett.* **1999,** 6845–6848.

12. The complete details of all reaction conditions, chemical correlations, X-ray diffraction analysis, computational calculations and physical and spectral data of all intermediates are described in the PhD Thesis of E. Falomir (University of Castellón, 1998).

13. Even though any one of the three silyl groups (TES, TBS and TBDPS) is suitable as a protecting group under the reaction conditions of the sequence **7→8→9→10**; here we describe only those esters **8** and **9** bearing a TBS group.

14. (a) Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.* **1993,** *58*, 3586–3588. (b) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996,** *61*, 5178–5179.

15. The formation of small amounts of the deformylated ester **9** during the oxidative cleavage of **8** could not be avoided: shorter reaction times only led to incomplete oxidation of **7**. However, the mixture of **8** and **9** may be used without separation in either of the subsequent reactions, thus improving the overall yields.

16. The formylated derivatives **8** are quite sensitive to alkaline media. Hydrolysis of **8** under even such mild conditions as potassium carbonate in MeOH at 0°C caused decomposition. The same result was observed when **8** (or **9**) was treated with tetra-*n*-butylammonium fluoride in THF.

17. Dihydroxy ester **10** (R′=Ph) showed NMR data identical with those reported: Wang, Z.-M.; Kolb, H. C.; Sharpless, K. B. *J. Org. Chem.* **1994,** *59*, 5104–5105.

18. (a) Palomo, C.; Aizpurua, J. M.; Cabré, F.; Cuevas, C.; Munt, S.; Odriozola, J. M. *Tetrahedron Lett.* **1994,** 2725–2728. (b) Ojima, I. *Acc. Chem. Res.* **1995,** *28*, 383–389. (c) Cativiela, C.; Díaz de Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1996,** *7*, 529–536. (d) Merino, P.; Castillo, E.; Franco, S.; Merchán, F. L.; Tejero, T. *Tetrahedron* **1998,** *54*, 12301–12322. (e) Brackenridge, I., Davies, S. G.; Fenwick, D. R.; Ichihara, O.; Polywka, M. E. C. *Tetrahedron* **1999,** *55*, 533–540. (f) Seki, M.; Matsumoto, K. *Synthesis* **1999,** 924.

19. Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, 9083–9086.

20. For the enolization of ketones with Chx_2BCl/tertiary amine to yield E boron enolates, see Ref. 10 and: (a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989,** *111*, 3441–3442. (b) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992,** *57*, 2716–2721. (c) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1992,** *57*, 3767–3772. (d) Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993,** *58*, 4182–4184. (e) Paterson, I.; Nowak, T. *Tetrahedron Lett.* **1996,** 8243–8246.

21. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

22. For recent theoretical studies on boron aldol reactions, see: (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990,** *55*, 481–493. (b) Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991,** *47*, 3471–3484. (c) Gennari, C.; Vieth, S.; Comotti, A.; Vulpetti, A.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1992,** *48*, 4439–4458. (d) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993,** *49*, 685–696.

23. Computational ab initio calculations have been performed by Dr J. Murga. The results will be disclosed in due time.

24. In the single case hitherto described of *syn* aldol formation of an α-alkoxy ketone with Chx_2BCl,[19] it has been suggested that initial formation of a five-membered chelate involving the boron and the two oxygen atoms, followed by stereoselective deprotonation by the tertiary amine, explain the formation of the putative *Z* enolate. This and other alternative explanations are now being studied by us at both the theoretical and the experimental level.

25. Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287–11314.