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PAPER

Double diastereoselection in *anti* aldol reactions mediated by dicyclohexylchloroborane between an L-erythrulose derivative and chiral aldehydes†‡

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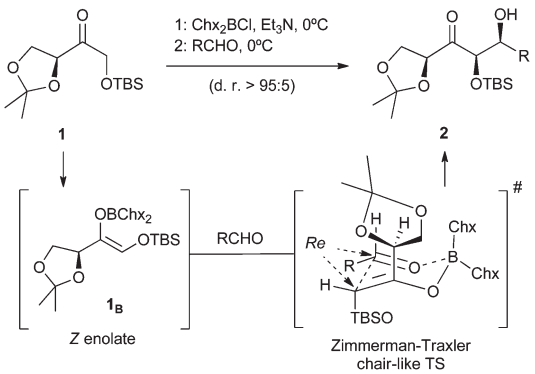
Anti aldol reactions of an L-erythrulose derivative with several α-chiral aldehydes mediated by dicyclohexylboron chloride are examined. Good yields and stereoselectivities are observed. The results are best explained when the reactions are assumed to occur *via* boat-like transition states with minimization of 1,3-allylic strain and avoidance of *syn* pentane interactions.

Introduction

The aldol reaction is a powerful and general method for the stereocontrolled construction of carbon–carbon bonds.[1] It may be performed through the use of various types of metal enolates or also in an organocatalytic, metal-free manner.[2,3] From the many enolate types investigated thus far, boron enolates have proven to be particularly versatile because of their good reactivity and high stereoselectivity.[4] In the last decade, we have been investigating the outcome of aldol reactions of boron enolates of protected L-erythrulose derivatives such as **1**, generated with Chx_2BCl (dicyclohexylboron chloride).[5] With these ketones, the latter reagent gives rise to the highly stereoselective formation of *syn* aldols **2** *via* the *Z* enolate[6] $\mathbf{1_B}$ in reactions with achiral aldehydes RCHO (Scheme 1).[7]

Subsequent to these initial investigations, we wondered whether or not the facial bias of chiral enolate $\mathbf{1_B}$ would be strong enough to overcome the inherent facial preferences of the carbonyl group in aldehydes having a stereocentre in the α-carbon atom (double diastereoselection).[1a–e] Therefore, we investigated the aldol reactions of $\mathbf{1_B}$ with a range of α-chiral aldehydes in both antipodal forms. In the initial study, the aldehydes had only carbon substituents (α-methyl aldehydes **3**) or else one oxygen (α-alkoxy aldehydes **4**) bound to the α-carbon atom (in all these aldehydes, P is a protecting group, and R is a variable fragment).[8]



Scheme 1 Aldol additions of a *Z* boron enolate of chiral ketone **1** to achiral aldehydes *via* a chair-like transition state (TS) (Chx = cyclohexyl; TBS = *tert*-butyldimethylsilyl).

The study was subsequently extended to the case of α-amino and α-fluoro aldehydes.[9] The results of all these aldol reactions are summarized in Scheme 2. The aldols depicted are the only diastereomers detected in the aldol reaction mixture by means of NMR (d.r. > 95 : 5). In all successful cases, a practically exclusive attack of the enolate *Re* face on the aldehyde carbonyl *Re* face was observed.[10] We explained the stereochemical course of these aldol reactions by assuming the generally accepted model of cyclic, six-membered transition states of the Zimmerman–Traxler type (Scheme 1).[11,12] In the case of α-chiral aldehydes, where issues of double diastereoselection are at work,[1a–c] we completed the mechanistic paradigm with the inclusion of the Felkin–Anh model and its subsequent refinements.[13,14] As

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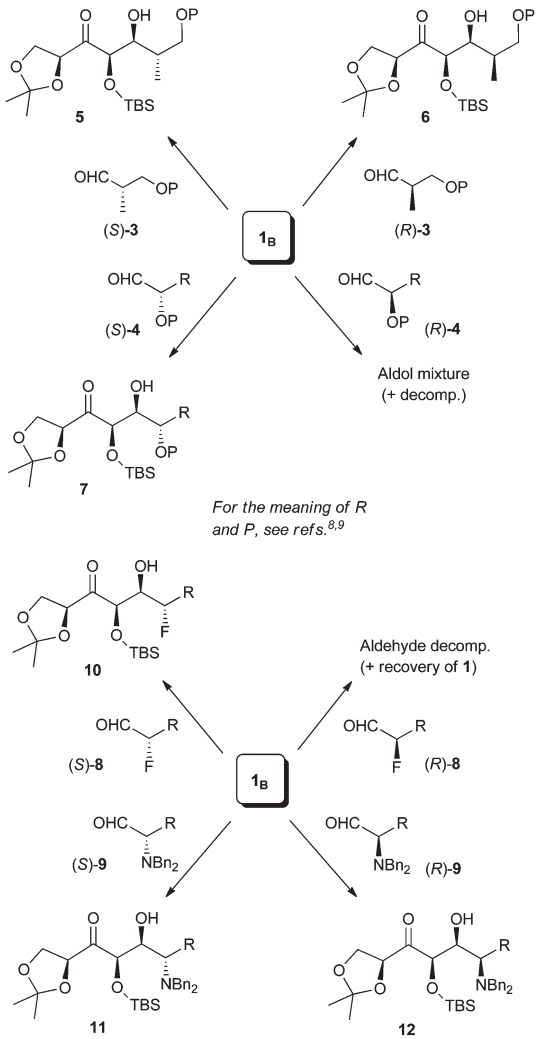
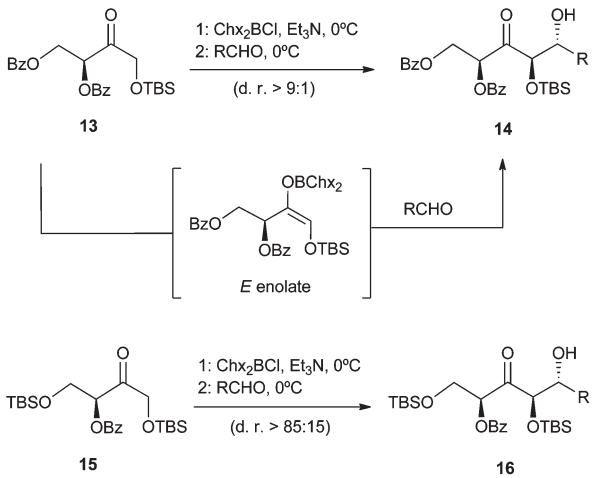
† Dedicated to the memory of Prof. Dr emerit. E. Vogel, University of Cologne, Germany, deceased March 31, 2011.

‡ Electronic supplementary information (ESI) available: Additional experimental procedures and tabulated spectral data of all correlation intermediates. Graphical NMR spectra of all new compounds (three PDF files). CCDC 285438, 762867, 762868, 764882, 764883, 766571. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25803j



Scheme 2 Aldol additions of enolate $\mathbf{1_B}$ to aldehydes (*R*)/(*S*)-**3**, (*R*)/(*S*)-**4**, (*R*)/(*S*)-**8** and (*R*)/(*S*)-**9** (Bn = benzyl).



Scheme 3 *Anti* aldol additions of boron enolates of chiral ketones **13** and **15** to achiral aldehydes (Bz = benzoyl).

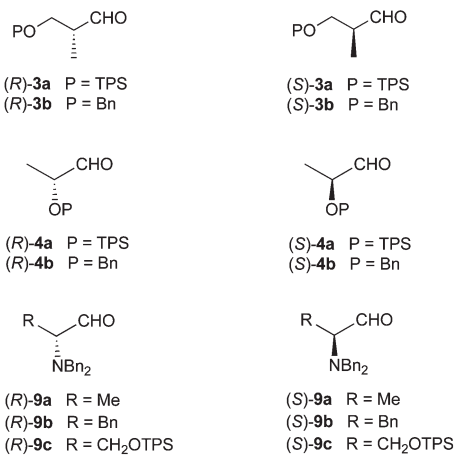


Fig. 1 α-Chiral aldehydes used in this study (TPS = *tert*-butyldiphenylsilyl).

matters evolved, however, we found that strict adherence to this model did not allow for a satisfactory account of all observed results, most particularly with aldehydes having highly electronegative atoms (F,O) bound to the α-carbon. In such cases, it was found that additional inclusion of features of the Cornforth model[15–17] provided a much better explanation.[8,9] This conclusion was further supported by means of density functional calculations.[9]

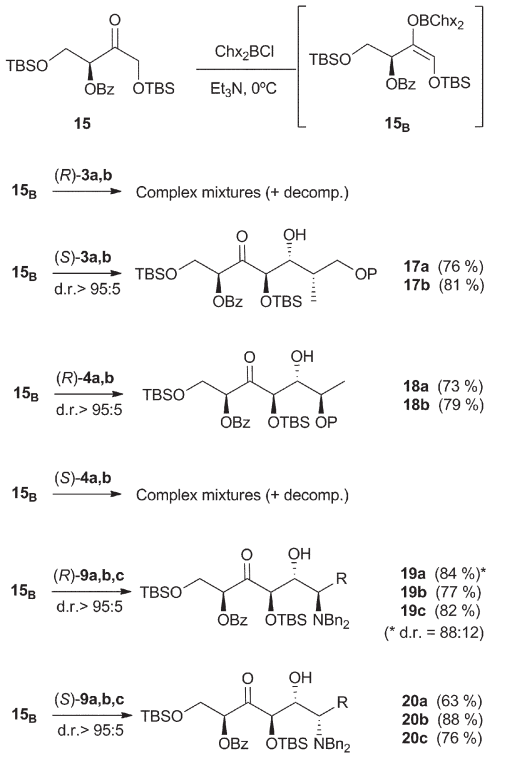
Shortly after beginning our research on boron aldol reactions with ketone **1**, and relying on findings of Paterson and coworkers,[6a] we wondered whether the replacement of one or more of the electron-donating *O*-protecting groups of **1** by electron-withdrawing counterparts would change the stereochemical course of the aldol reaction from *syn* to *anti*. Indeed, and in line with Paterson's idea, chiral ketone **13**, which bears two benzoyl protecting groups, was found to stereoselectively give *anti* aldols **14** with achiral aldehydes (Scheme 3),[18] most likely through the corresponding *E* boron enolate.[19] Later quantum-mechanical studies of our group provided the theoretical basis for this mechanistic assumption.[5d] In a more recent development, the dibenzoylated ketone **13** has been replaced by its monobenzoylated counterpart **15**, which is easier to prepare and yields *anti* aldols **16** with similar degrees of stereoselectivity.[20]

The purpose of the present investigation is the study of the double diastereoselection in *anti* aldol reactions of ketone **15** with α-chiral aldehydes.

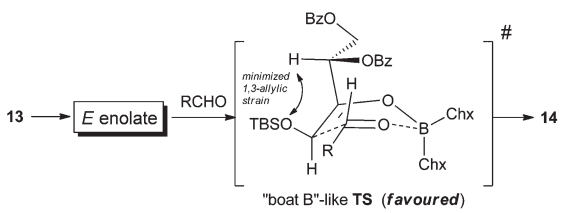
Results and discussion

The α-chiral aldehydes (*R*)/(*S*)-**3**, (*R*)/(*S*)-**4** and (*R*)/(*S*)-**9**, used in the present study (Fig. 1), are also those of our previous publications[8,9] and have been prepared by means of the same procedures (α-fluoro aldehydes **8** have not been included in the present study). The results of the aldol reactions are presented in Scheme 4.

Ketone **15** is assumed to be first converted into *E* enolate $\mathbf{15_B}$. The latter then reacts with the aldehydes to yield the *anti* aldols **17–20**, obtained as essentially single diastereoisomers in the majority of cases. Exceptions to this behaviour were aldehydes (*R*)-**3a,b** and (*S*)-**4a,b**, which gave complex mixtures, accompanied by ill-defined decomposition products.



Scheme 4 Aldol additions of an *E* enolate of ketone **15** to aldehydes (*R*)/(*S*)-**3a,b**, (*R*)/(*S*)-**4a,b** and (*R*)/(*S*)-**9a,b,c**. *d.r.* > 95 : 5 unless otherwise stated (for the meaning of P and R, see Fig. 1).



Scheme 5 Proposed TS for the aldol addition step of the *E* boron enolate of ketone **13** and achiral aldehydes RCHO.

Furthermore, aldol **19a** was obtained as an 88 : 12 mixture (for the methods used to establish the stereostructures of these aldols, see the ESI†).

For a mechanistic explanation of the stereochemical course of these reactions, we cannot directly adapt the chair-like Zimmerman–Traxler model used in our previous publications that discussed the formation of *syn* aldols *via Z* enolates.[8,9] Indeed, theoretical calculations of our group have led to the proposal that *anti* aldol reactions of ketone **13** with achiral aldehydes mediated by Chx_2BCl take place through a transition structure (TS) of the "boat B" type (Scheme 5).[5d,12g] One salient feature of this TS is the arrangement of the groups around the stereocentre in the enolate moiety in such a way as to minimize the 1,3-allylic strain[21] within the enolate *E* olefinic moiety. As a consequence, the benzoate points inside the cyclic TS but, due to the boat shape of the latter, this does not lead to a steric crowding with the cyclohexyl ligands at the boron atom (compare with the chair-like TS in Scheme 1).

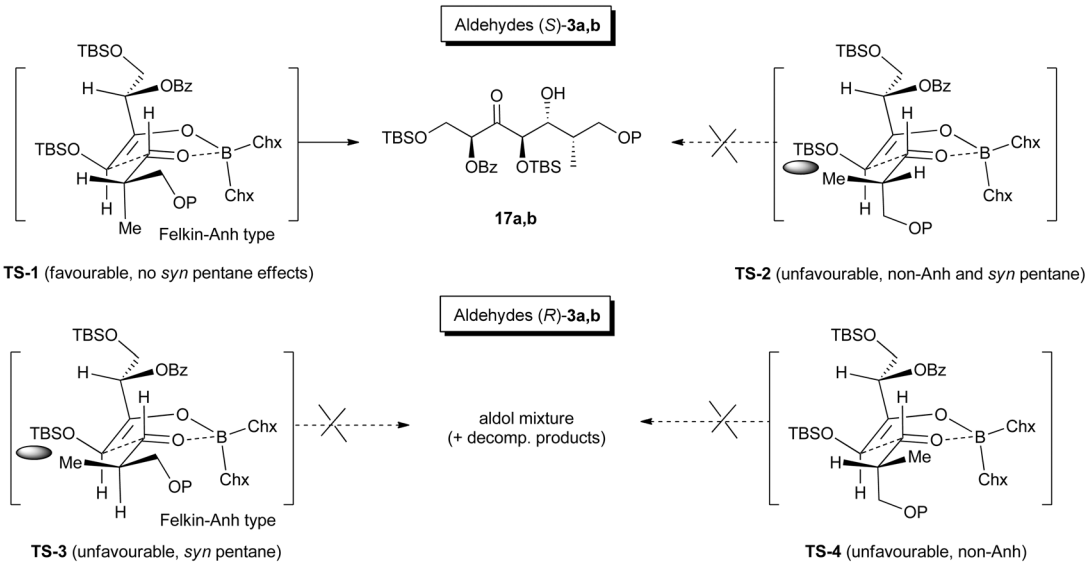
If we wish to extend this mechanistic view to the aldol reactions of ketone **15** with α-chiral aldehydes (Scheme 4), it is also necessary to add to the general model all the other factors which were taken into account in our previous papers[8,9] on aldol reactions of ketone **1**, *i.e.* the Felkin–Anh and Cornforth models.[13–17]

The case of α-methyl aldehydes (*R*)- and (*S*)-**3a,b** will be studied first. According to Scheme 4, aldehydes (*S*)-**3a,b** reacted with enolate $\mathbf{15_B}$ to yield *anti* aldols **17a,b** with good yields and excellent diastereoselectivity. In contrast, the same reaction with aldehydes (*R*)-**3a,b** only gave aldol mixtures, accompanied by decomposition products.

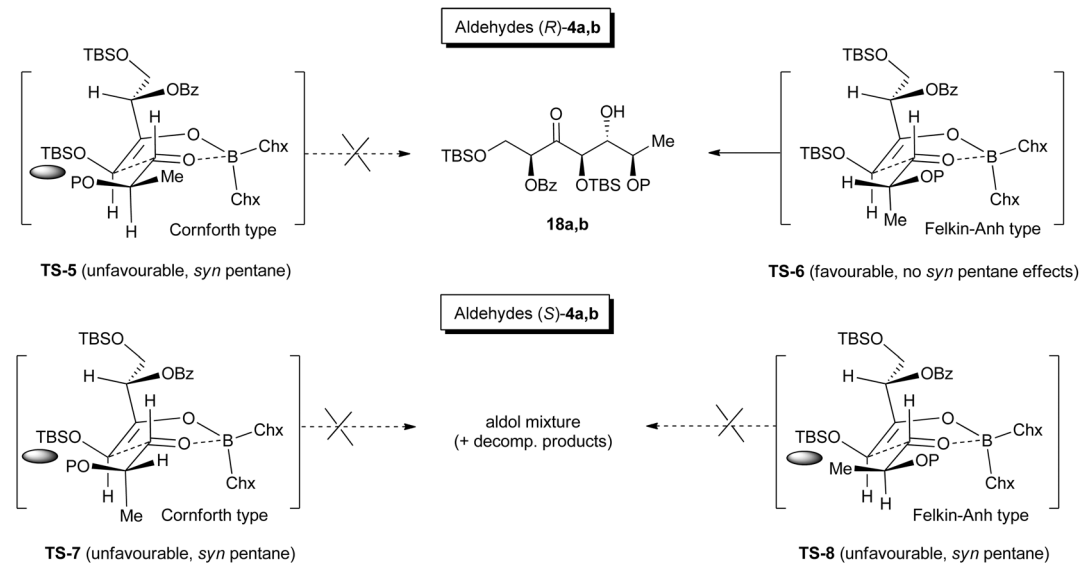
If the stereochemical model of Scheme 5 is applied to the reactions of $\mathbf{15_B}$ with aldehydes (*R*)- and (*S*)-**3a,b**, we obtain the four boat-like transition structures (**TS-1** to **TS-4**) depicted in Scheme 6. The formation of aldols **17a,b** in the case of (*S*)-**3a,b** can be reasonably explained with transition structure **TS-1**. It can be seen that the spatial arrangement of the three groups at the α-carbon of the aldehyde (H, Me, CH_2OP) closely adheres to the Felkin–Anh model (*anti* orientation of the bulky CH_2OP group and the attacking nucleophile). Since no unfavourable steric features are present in **TS-1**, it is not surprising that these reactions take place with good results, both in terms of yield and stereoselectivity, to yield *anti* aldols **17a,b**. Rotation of the aldehyde C_α–CO bond in **TS-1** gives rise to the alternative transition structure **TS-2**, which would yield the same final product. However, this TS is markedly higher in energy contents, as it shows two unfavourable features: (a) a non-Anh arrangement[22] of the three groups at the α-carbon of the aldehyde. (b) a *syn* pentane interaction[23,24] between the Me and OTBS groups. Particularly the latter effect has been shown to be quantitatively very important in aldol and allylation reactions, often overriding the stereoelectronic preference associated with a Felkin–Anh geometry.[8,9,23] In consequence, we may assume than the aldol reactions of $\mathbf{15_B}$ with aldehydes (*S*)-**3a,b** take place only through **TS-1**.

The situation is different in the case of aldehydes (*R*)-**3a,b**, which react with $\mathbf{15_B}$ to give mixtures of aldols together with decomposition products (Scheme 4). In Scheme 6, a plausible explanation for this result is proposed. The reaction may take place through either **TS-3** or **TS-4**: **TS-3** is of the Felkin–Anh type but also shows an unfavourable *syn* pentane interaction, whereas **TS-4** is of the non-Anh type. Both reactions therefore must traverse unfavourable transition structures and become accordingly slower, with the expected loss of stereoselectivity and increased probability of decomposition pathways.

A similar situation is found in the case of α-oxygenated aldehydes (*R*)- and (*S*)-**4a,b**, even though the *R* enantiomers are those reacting efficiently here, whereas the *S* enantiomers give complex aldol mixtures and decomposition products (Scheme 4). As above, four boat-like transition structures (**TS-5** to **TS-8**), depicted in Scheme 7, may be drawn for these reactions. In the same line of reasoning as above, the successful reactions of aldehydes (*R*)-**4a,b** are proposed to occur through transition structures like **TS-6**, which is of the Felkin–Anh type and does not display unfavourable steric features. In contrast, **TS-5** shows an unfavourable *syn* pentane effect. The same effects are also seen in transition structures **TS-7** and **TS-8**, which should be relevant for the reactions of aldehydes (*S*)-**4a,b**. It is thus not surprising



Scheme 6 Proposed TSs for the aldol addition step of boron enolate $\mathbf{15_B}$ to α-methyl aldehydes (*R*)- and (*S*)-**3a,b**.



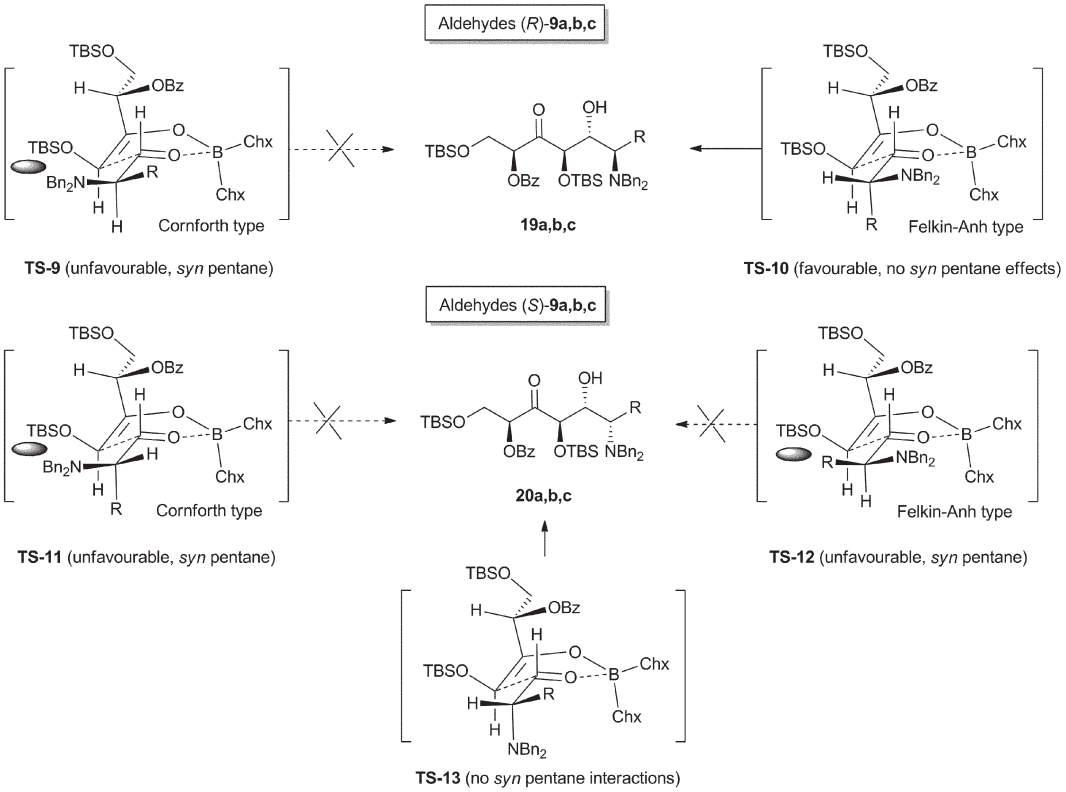
Scheme 7 Proposed TSs for the aldol addition step of boron enolate $\mathbf{15_B}$ to α-oxygenated aldehydes (*R*)- and (*S*)-**4a,b**.

that the latter reactions yield complex aldol mixtures and decomposition products. It is also worth mentioning that, while **TS-8** belongs to the Felkin–Anh type[13] (see above), **TS-5** and **TS-7** belong to the Cornforth type (*anti* orientation of the electronegative OP group and the aldehyde C═O bond).[15–17] Nonetheless, the energetically important contribution of the *syn* pentane interaction is able to override the aforementioned effects.

The aldol reactions of the α-amino aldehydes **9a,b,c** showed a difference with the previous ones. In this case, both (*R*)- and (*S*)-**9a,b,c** reacted with enolate $\mathbf{15_B}$ to yield aldol adducts (**19** and **20**, respectively) with good yields and, in most cases, high diastereoselectivity. An application of the previous models to the reactions of these aldehydes would yield the transition structures **TS-9** to **TS-12**, all of them depicted in Scheme 8. The aldol reactions of aldehydes (*R*)-**9a,b,c** to yield **19a,b,c** can be thought to occur *via* **TS-10**, which is of the Felkin–Anh type and does not display unfavourable steric features. The alternative, Cornforth-type **TS-9** shows a *syn* pentane effect and can thus be ruled out.

For the aldol reactions of aldehydes (*S*)-**9a,b,c**, **TS-11** (Cornforth) and **TS-12** (Felkin–Anh) might be considered suitable TSs. However, both show a *syn* pentane interaction. Accordingly, and as observed for aldehydes (*S*)-**4a,b**, only complex aldol mixtures and decomposition products should be expected. In contrast with this prediction, aldols **20a,b,c** are diastereoselectively formed with good yields.

A plausible explanation for this result is the assumption of the alternative **TS-13**, which is devoid of the energetically unfavourable *syn* pentane effects, even if it shows neither the



Scheme 8 Proposed TSs for the aldol addition step of boron enolate $\mathbf{15_B}$ to α-amino aldehydes (*R*)- and (*S*)-**9a,b,c**.

stereoelectronic benefit of the Felkin–Anh geometry nor the favourable Cornforth-like *anti* arrangement of the polar C═O and C–N bonds. Nevertheless, it has been commented above that *syn* pentane effects have been shown to be quantitatively very important in aldol and allylation reactions, often overriding the stereoelectronic preference associated to a Felkin–Anh geometry.[8,9,23] Moreover, the lower electronegativity of nitrogen as compared with oxygen makes the energetic advantage of the Cornforth geometry in α-amino aldehydes less important than in α-oxygenated aldehydes. Indeed, as previously observed in the aldol additions of the *Z* enolate $\mathbf{1_B}$, Cornforth-like TSs were found relevant mainly for aldehydes bearing highly electronegative atoms (O,F) in the α carbon but even in that case, the minimization of the dipolar repulsion was not able to override a *syn* pentane interaction.[8,9]

Experimental

General

NMR spectra were recorded at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) in $CDCl_3$ solution at 25 °C, if not otherwise indicated, with the solvent signals as internal reference. ^{13}C NMR signal multiplicities were determined with the DEPT pulse sequence. Mass spectra were run in the EI (70 eV), the FAB (*m*-nitrobenzyl alcohol matrix) or the electrospray (ESMS) mode. IR data, which were measured as films on NaCl plates (oils) or as KBr pellets (solids), are given only when relevant functions (C═O, OH) are present. Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere (all except those involving water in the reaction medium) were carried out under dry N_2 with flame-dried glassware. Commercial reagents were used as received. THF and Et_2O were freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Toluene was freshly distilled from sodium wire. Tertiary amines were freshly distilled from KOH. Unless detailed otherwise, "work-up" means pouring the reaction mixture into brine, *followed by extraction with the solvent indicated in parenthesis*. If the reaction medium was acidic, an additional washing of the organic layer with 5% aq $NaHCO_3$ was performed. If the reaction medium was basic, an additional washing with aq NH_4Cl was performed. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings combined with the main organic layer. The latter was dried over anhydrous Na_2SO_4 and the solvent was eliminated under reduced pressure. Column chromatography of the residue on a silica gel column (60–200 μm) was performed with elution with the indicated solvent mixture.

General experimental procedure for aldol additions of ketone 15 mediated by dicyclohexylboron chloride. Chx_2BCl (neat, 395 μL, *ca.* 1.8 mmol) was added under Ar *via* syringe to an ice-cooled solution of Et_3N (280 μL, 2 mmol) in anhydrous Et_2O (5 mL). Erythrulose derivative **15** (453 mg, 1 mmol) was dissolved in anhydrous Et_2O (5 mL) and added dropwise *via* syringe to the reagent solution. The reaction mixture was then stirred for 30 min and then cooled to −78 °C. After dropwise addition of a solution of the appropriate aldehyde[8,9] (4 mmol) in

anhydrous ether (6 mL), the reaction mixture was stirred at −78 °C for 5 h. Then phosphate buffer solution (pH 7, 6 mL) and MeOH (6 mL) were added, 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). Removal of volatiles under reduced pressure and column chromatography of the residue on silica gel (hexanes–EtOAc mixtures) afforded the aldol addition product. Yields and diastereoisomeric ratios are indicated in Scheme 4.

(2*S*,4*R*,5*R*,6*S*)-2-(Benzoyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-6-methylheptan-3-one (17a). Oil: $[\alpha]_D$ +2.2 (*c* 1.1; $CHCl_3$); IR ν_{max} 3490 (br, OH), 1728 (br, C═O) (cm^{-1}); ^1H NMR δ 8.10 (2H, br d, $J \sim$ 7.5 Hz; aromatic), 7.70–7.65 (4H, m; aromatic), 7.57 (1H, br t, $J \sim$ 7.5 Hz; aromatic), 7.45–7.35 (8H, br m; aromatic), 5.81 (1H, dd, J = 6.3, 3.3 Hz; H-2), 4.47 (1H, d, J = 8 Hz; H-4), 4.25–4.20 (2H, m; H-1/H-5), 4.12 (1H, dd, J = 11.2, 6.3 Hz; H-1′), 3.76 (1H, dd, J = 10, 4.3 Hz; H-7), 3.70 (1H, dd, J = 10, 5.5 Hz; H-7′), 3.30 (1H, br s; OH), 2.05 (1H, br m; H-6), 1.06 (9H, s; Me_3CSi), 0.96 (3H, d, J = 7 Hz; *Me*-C6), 0.92 (9H, s; Me_3CSi), 0.88 (9H, s; Me_3CSi), 0.10 (3H, s; *Me*Si), 0.09 (3H, s; *Me*Si), 0.08 (3H, s; *Me*Si), 0.07 (3H, s; *Me*Si); ^{13}C NMR δ 206.5, 166.1, 133.3, 133.2, 129.4, 19.2, 18.3, 18.1 (quat C), 135.6 (×2), 135.5 (×2), 133.2 (×2), 129.9 (×2), 129.7 (×2), 128.4 (×2), 127.7 (×3), 78.2, 77.6, 75.0, 35.7 (CH), 68.3, 62.4 (CH_2), 26.9 (×3, Me_3CSi), 25.8 (×6, 2 Me_3CSi), 9.6 (*Me*-C6), −4.4 (*Me*Si), −5.0 (*Me*Si), −5.4 (×2, 2 *Me*Si); HR EIMS *m*/*z* (% rel. int.) 721.3425 (M^+ − *t*Bu, 2), 269 (22), 105 (100), calcd for $C_{43}H_{66}O_7Si_3$ − *t*Bu, 721.3412.

(2*S*,4*R*,5*R*,6*S*)-2-(Benzoyloxy)-7-(benzyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-5-hydroxy-6-methylheptan-3-one (17b). Oil: $[\alpha]_D$ −2.2 (*c* 1.4; $CHCl_3$); IR ν_{max} (cm^{-1}): 3490 (br, OH), 1726 (br, C═O); ^1H NMR (500 MHz) δ 8.10 (2H, br d, $J \sim$ 7.5 Hz; aromatic), 7.57 (1H, br t, $J \sim$ 7.5 Hz; aromatic), 7.41 (2H, br t, $J \sim$ 7.5 Hz; aromatic), 7.40–7.25 (5H, br m; aromatic), 5.79 (1H, br t, $J \sim$ 4.3 Hz; H-2), 4.50–4.45 (3H, m; H-4/benzyl), 4.15–4.10 (3H, m; H-1/H-1′/H-5), 3.55–3.50 (2H, m; H-7/H-7′), 3.20 (1H, d, J = 5 Hz; OH), 2.08 (1H, br m; H-6), 0.97 (3H, d, J = 7 Hz; *Me*-C6), 0.88 (9H, s; Me_3CSi), 0.86 (9H, s; Me_3CSi), 0.08 (6H, s; 2 *Me*Si), 0.06 (3H, s; *Me*Si), 0.05 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 206.6, 166.0, 138.3, 129.5, 18.3, 18.1 (quat C), 133.3 (×2), 130.0 (×2), 128.4 (×3), 127.6 (×3), 78.6, 78.1, 74.6, 34.3 (CH), 74.3, 73.2, 62.7 (CH_2), 25.8 (×6, 2 Me_3CSi), 10.5 (*Me*-C6), −4.4 (*Me*Si), −5.0 (*Me*Si), −5.4 (×2, 2 *Me*Si); HR FABMS *m*/*z* 631.3476 (M + H^+). Calcd for $C_{34}H_{55}O_7Si_2$, 631.3486.

(2*S*,4*R*,5*R*,6*R*)-2-(Benzoyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-6-(*tert*-butyldiphenylsilyloxy)-5-hydroxyheptan-3-one (18a). Oil: $[\alpha]_D$ −2 (*c* 2.2; $CHCl_3$); IR ν_{max} (cm^{-1}): 3470 (br, OH), 1729 (br, C═O); ^1H NMR (500 MHz) δ 8.11 (2H, br d, $J \sim$ 7.5 Hz; aromatic), 7.72 (2H, br t, $J \sim$ 7 Hz; aromatic), 7.60 (1H, br t, $J \sim$ 7.5 Hz; aromatic), 7.50–7.25 (10H, br m; aromatic), 5.85 (1H, br t, $J \sim$ 4.5 Hz; H-2), 4.70 (1H, d, J = 7 Hz; H-4), 4.20–4.15 (2H, m; H-1/H-1′), 4.10 (1H, br quint, $J \sim$ 5.5 Hz; H-6), 3.90 (1H, br t, $J \sim$ 5.5 Hz; H-5), 2.90 (1H, br s; OH), 1.08 (9H, s; Me_3CSi), 1.05 (3H, d, J = 6.5 Hz; H-7), 0.92 (9H, s; Me_3CSi), 0.86 (9H, s; Me_3CSi), 0.13 (3H, s; *Me*Si), 0.10 (6H, s; 2× *Me*Si), 0.07 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 205.8, 165.9, 134.2, 133.2, 129.6, 19.2, 18.3, 18.0 (quat C), 135.7 (×4), 129.9 (×2), 129.7, 129.5 (×2), 128.4 (×2), 127.6 (×2), 127.5 (×2), 79.0, 78.0, 76.6, 69.7 (CH), 62.2 (CH_2), 26.9 (×3, Me_3CSi), 25.8 (×6, 2 Me_3CSi), 16.9 (C7), −4.4 (*Me*Si), −5.0 (*Me*Si), −5.4 (×2, 2 *Me*Si); HR EIMS *m*/*z* (% rel. int.) 707.3249 (M^+ − *t*Bu, 1), 255 (90), 105 (100). Calcd for $C_{42}H_{64}O_7Si_3$ − *t*Bu, 707.3255.

(2*S*,4*R*,5*R*,6*R*)-2-(Benzoyloxy)-6-(benzyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-5-hydroxyheptan-3-one (18b). Oil: $[\alpha]_D$ −11.2 (*c* 1.15; $CHCl_3$); IR ν_{max} (cm^{-1}): 3470 (br, OH), 1727 (br, C═O); ^1H NMR (500 MHz) δ 8.10 (2H, br d, $J \sim$ 7.5 Hz; aromatic), 7.60 (1H, br t, $J \sim$ 7.5 Hz; aromatic), 7.48 (2H, br t, $J \sim$ 7.5 Hz; aromatic), 7.35–7.25 (5H, br m; aromatic), 5.65 (1H, dd, J = 5.5, 3 Hz; H-2), 4.75 (1H, d, J = 4.4 Hz; H-4), 4.46 (1H, d, J = 11.7 Hz; benzyl), 4.32 (1H, d, J = 11.7 Hz; benzyl), 4.04 (1H, dd, J = 11.3, 5.5 Hz; H-1), 3.96 (1H, dd, J = 11.3, 3 Hz; H-1′), 3.91 (1H, br td, $J \sim$ 8.5, 4.4 Hz; H-5), 3.56 (1H, br dq, J = 8.5, 6.5 Hz; H-6), 2.60 (1H, d, J = 9 Hz; OH), 1.24 (3H, d, J = 6.5 Hz; H-7), 0.98 (9H, s; Me_3CSi), 0.85 (9H, s; Me_3CSi), 0.18 (3H, s; *Me*Si), 0.12 (3H, s; *Me*Si), 0.03 (3H, s; *Me*Si), 0.00 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 203.2, 165.8, 138.2, 129.5, 19.2, 18.3, 18.2 (quat C), 133.3, 129.8 (×2), 128.5 (×2), 128.2 (×2), 128.0 (×2), 127.5, 78.8, 78.4, 76.2, 70.6 (CH), 74.0, 62.3 (CH_2), 25.9 (×3, Me_3CSi), 25.7 (×3, Me_3CSi), 15.9 (C7), −4.4 (*Me*Si), −5.1 (*Me*Si), −5.4 (×2, 2 *Me*Si); HR FABMS *m*/*z* 617.3353 (M + H^+). Calcd for $C_{33}H_{53}O_7Si_2$, 617.3329.

(2*S*,4*R*,5*R*,6*R*)-2-(Benzoyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-6-(*N*,*N*-dibenzylamino)-5-hydroxyheptan-3-one (19a)

Obtained as an 88 : 12 mixture with a diastereoisomer. Chromatographic separation gave the major diastereoisomer **20a**: oil: $[\alpha]_D$ +11.5 (*c* 1.18; $CHCl_3$); IR ν_{max} (cm^{-1}): 3460 (br, OH), 1726 (br, C═O); ^1H NMR (500 MHz) δ 8.19 (2H, br d, $J \sim$ 8 Hz; aromatic), 7.66 (1H, br t, $J \sim$ 7.5 Hz; aromatic), 7.54 (2H, br t, $J \sim$ 7.5 Hz; aromatic), 7.35–7.15 (10H, br m; aromatic), 5.77 (1H, br t, $J \sim$ 4 Hz; H-2), 4.44 (1H, m; H-5), 4.30 (1H, d, J = 7.3 Hz; H-4), 4.18 (1H, dd, J = 11, 4.8 Hz; H-1), 4.11 (1H, dd, J = 11, 3.5 Hz; H-1′), 3.86 (2H, d, J = 14.2 Hz, *N*-benzyl CH_2), 3.68 (2H, d, J = 14.2 Hz, *N*-benzyl CH_2), 3.30 (1H, br s; OH), 3.05 (1H, qd, J = 6.8, 2.5 Hz; H-6), 1.13 (3H, d, J = 6.8 Hz; H-7), 0.90 (9H, s; Me_3CSi), 0.73 (9H, s; Me_3CSi), 0.12 (3H, s; *Me*Si), 0.09 (3H, s; *Me*Si), −0.07 (3H, s; *Me*Si), −0.13 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 206.0, 165.8, 140.5 (×2), 129.5, 18.3, 18.0 (quat C), 133.5, 130.0 (×2), 128.5 (×2), 128.4 (×4), 128.1 (×4), 126.5 (×2), 79.9, 78.1, 75.0, 53.2 (CH), 63.3, 54.6 (×2) (CH_2), 25.7 (×6, 2 Me_3CSi), 8.0 (C7), −4.8 (*Me*Si), −5.1 (*Me*Si), −5.5 (×2, 2 *Me*Si); HR FABMS *m*/*z* 706.3971 (M + H^+). Calcd for $C_{40}H_{60}NO_6Si_2$, 706.3959.

(2*S*,4*R*,5*R*,6*R*)-2-(Benzoyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-6-(*N*,*N*-dibenzylamino)-5-hydroxy-7-phenylheptan-3-one (19b). Oil: $[\alpha]_D$ +7.4 (*c* 1.65; $CHCl_3$); IR ν_{max} (cm^{-1}): 3430 (br, OH), 1727 (br, C═O); ^1H NMR (500 MHz) δ 8.20 (2H, br d, $J \sim$ 7.5 Hz; aromatic), 7.64 (1H, br d, $J \sim$ 7.5 Hz; aromatic), 7.53 (2H, br t, J = 7.5 Hz; aromatic), 7.30–7.00 (15H, br m; aromatic), 5.84 (1H, br t, $J \sim$ 4 Hz; H-2), 4.70 (1H, d, J = 8 Hz;

H-4), 4.34 (1H, br d, J = 8 Hz; H-5), 4.26 (1H, dd, J = 10.8, 4 Hz; H-1), 4.14 (1H, dd, J = 10.8, 4 Hz; H-1′), 3.95 (2H, d, $J \sim$ 14.7 Hz, *N*-benzyl CH_2), 3.60 (2H, br d, $J \sim$ 14.7 Hz, *N*-benzyl CH_2), 3.50 (1H, br s; OH), 3.22 (1H, br dd, $J \sim$ 10.2, 4.1 Hz; H-6), 3.10 (1H, dd, J = 14.3, 10.2 Hz; H-7), 2.94 (1H, dd, J = 14.3, 4.1 Hz; H-7′), 0.95 (9H, s; Me_3CSi), 0.71 (9H, s; Me_3CSi), 0.18 (3H, s; *Me*Si), 0.14 (3H, s; *Me*Si), −0.09 (3H, s; *Me*Si), −0.14 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 206.6, 165.6, 140.4, 140.2 (×2), 129.4, 18.4, 18.1 (quat C), 133.6, 130.1, 130.0, 128.6 (×2), 128.3 (×4), 128.0 (×5), 127.9 (×3), 126.4 (×2), 125.8, 80.1, 77.6, 71.5, 59.2 (CH), 63.5, 54.3 (×2), 31.2 (CH_2), 25.9 (×3, Me_3CSi), 25.8 (×3, Me_3CSi), −4.7 (*Me*Si), −5.0 (*Me*Si), −5.4 (*Me*Si) −5.5 (*Me*Si); HR EIMS m/z (% rel. int.) 724.3553 (M^+ − *t*Bu, 1), 300 (76), 91 (100). Calcd for $C_{46}H_{63}NO_6Si_2$ − *t*Bu, 724.3616.

(2*S*,4*R*,5*R*,6*R*)-2-(Benzoyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-6-(*N*,*N*-dibenzylamino)-5-hydroxyheptan-3-one (19c). Oil: $[\alpha]_D$ −6 (*c* 1.3; $CHCl_3$); IR ν_{max} (cm^{-1}): 3460 (br, OH), 1725 (br, C═O); ^{1}H NMR (500 MHz) δ 8.22 (2H, br d, $J \sim$ 8 Hz; aromatic), 7.80 (4H, br d, $J \sim$ 7.5 Hz; aromatic), 7.70–7.20 (19H, br m; aromatic), 5.94 (1H, br t, $J \sim$ 4.5 Hz; H-2), 4.58 (2H, m; H-4/H-5), 4.22 (2H, m; H-1/H-1′), 4.17 (1H, dd, J = 11.5, 6 Hz; H-7), 4.08 (1H, dd, J = 11.5, 4 Hz; H-7′), 3.97, 3.93 (4H, AB system, J = 14.5 Hz, 2 *N*-benzyl CH_2), 3.60 (1H, br s; OH), 3.25 (1H, m; H-6), 1.18 (9H, s; Me_3CSi), 0.95 (9H, s; Me_3CSi), 0.80 (9H, s; Me_3CSi), 0.17 (3H, s; *Me*Si), 0.14 (3H, s; *Me*Si), −0.01 (3H, s; *Me*Si), −0.12 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 205.4, 165.7, 140.1 (×2), 132.9, 132.8, 129.7, 19.0, 18.3, 18.1 (quat C), 135.7 (×4), 133.3, 130.0 (×4), 128.4 (×4), 128.1 (×4), 127.6 (×4), 126.5 (×4), 79.8, 78.2, 74.0, 58.9 (CH), 62.8, 62.2, 55.3 (×2) (CH_2), 26.9 (×3, Me_3CSi), 25.8 (×6, 2 Me_3CSi), −4.8 (*Me*Si), −4.9 (*Me*Si), −5.4 (×2) (*Me*Si); HR ESMS m/z 960.5086 (M + H^+). Calcd for $C_{56}H_{78}NO_7Si_3$, 960.5087.

(2*S*,4*R*,5*R*,6*S*)-2-(Benzoyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-6-(*N*,*N*-dibenzylamino)-5-hydroxyheptan-3-one (20a). Oil: $[\alpha]_D$ + 35.1 (*c* 2.25; $CHCl_3$); IR ν_{max} (cm^{-1}): 3420 (br, OH), 1724 (br, C═O); ^{1}H NMR (500 MHz) δ 8.11 (2H, br d, $J \sim$ 7.5 Hz; aromatic), 7.58 (1H, br t, $J \sim$ 7.5 Hz; aromatic), 7.46 (2H, br t, $J \sim$ 7.5 Hz; aromatic), 7.30–7.20 (10H, br m; aromatic), 5.97 (1H, br t, $J \sim$ 4 Hz; H-2), 4.60 (1H, br s; H-4), 4.20 (1H, br s; OH), 4.18 (1H, dd, J = 11.3, 5 Hz; H-1), 4.09 (1H, dd, J = 11.3, 2.7 Hz; H-1′), 4.02 (1H, br d, J = 9.5 Hz; H-5), 3.77 (2H, d, J = 13.2 Hz, *N*-benzyl CH_2), 3.30 (2H, d, J = 13.2 Hz, *N*-benzyl CH_2), 2.94 (1H, dq, J = 7.5, 6.8 Hz; H-6), 0.97 (3H, d, J = 6.8 Hz; H-7), 0.85 (9H, s; Me_3CSi), 0.83 (9H, s; Me_3CSi), 0.06 (6H, s; 2 *Me*Si), 0.02 (3H, s; *Me*Si), −0.28 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 204.8, 165.5, 138.9 (×2), 129.8, 18.2 (×2) (quat C), 133.2, 129.9 (×2), 129.2 (×4), 128.4 (×4), 128.3 (×2), 127.7 (×2), 79.8, 77.9, 72.5, 55.0 (CH), 62.5, 53.4 (×2) (CH_2), 25.9 (×3, Me_3CSi), 25.7 (×3, Me_3CSi), 8.5 (C7), −4.6 (×2, 2 *Me*Si), −5.4 (×2, 2 *Me*Si); HR FABMS m/z 706.3947 (M + H^+). Calcd for $C_{40}H_{60}NO_6Si_2$, 706.3959.

(2*S*,4*R*,5*R*,6*S*)-2-(Benzoyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-6-(*N*,*N*-dibenzylamino)-5-hydroxy-7-phenylheptan-3-one (20b). Oil: $[\alpha]_D$ +14.4 (*c* 1; $CHCl_3$); IR ν_{max} (cm^{-1}): 3370 (br, OH), 1724 (br, C═O); ^{1}H NMR (500 MHz) δ 8.16 (2H, br d, $J \sim$ 7.5 Hz; aromatic), 7.62 (1H, br d, $J \sim$ 7.5 Hz; aromatic), 7.48 (2H, br t, J = 7.5 Hz; aromatic), 7.40 (4H, m; aromatic), 7.30–7.10 (11H, br m; aromatic), 5.95 (1H, br t, $J \sim$ 4 Hz; H-2), 4.74 (1H, d, J = 2 Hz; H-4), 4.50 (1H, br s; OH), 4.20 (1H, dd, J = 11.3, 5.3 Hz; H-1), 4.15 (1H, dd, J = 11.3, 3 Hz; H-1′), 4.00 (1H, dd, J = 9.5, 2 Hz; H-5), 3.75 (2H, br d, $J \sim$ 13 Hz, *N*-benzyl CH_2), 3.41 (1H, br td, $J \sim$ 9.5, 3 Hz; H-6), 3.33 (2H, br d, $J \sim$ 13 Hz, *N*-benzyl CH_2), 2.86 (1H, dd, J = 14, 3 Hz; H-7), 2.78 (1H, dd, J = 14, 10 Hz; H-7′), 0.92 (9H, s; Me_3CSi), 0.88 (9H, s; Me_3CSi), 0.12 (3H, s; *Me*Si), 0.09 (3H, s; *Me*Si), 0.05 (3H, s; *Me*Si), −0.10 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 205.3, 165.4, 140.2, 139.0 (×2), 129.6, 18.3, 18.2 (quat C), 133.1, 130.0 (×2), 129.7 (×2), 129.2 (×4), 128.4 (×2), 128.3 (×2), 128.2 (×4), 127.1 (×2), 126.3, 79.9, 78.0, 72.0, 61.0 (CH), 62.6, 54.1 (×2), 33.9 (CH_2), 25.9 (×3, Me_3CSi), 25.7 (×3, Me_3CSi), −4.8 (*Me*Si), −5.1 (*Me*Si), −5.5 (×2, 2 *Me*Si); HR EIMS m/z (% rel. int.) 724.3692 (M^+ − *t*Bu, 9), 300 (32), 91 (100). Calcd for $C_{46}H_{63}NO_6Si_2$−*t*Bu, 724.3616.

(2*S*,4*R*,5*R*,6*S*)-2-(Benzoyloxy)-1,4-bis-(*tert*-butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-6-(*N*,*N*-dibenzylamino)-5-hydroxyheptan-3-one (20c). Oil: $[\alpha]_D$ −2 (*c* 1.1; $CHCl_3$); IR ν_{max} (cm^{-1}): 3460 (br, OH), 1726 (br, C═O); ^{1}H NMR (500 MHz) δ 8.08 (2H, br d, $J \sim$ 8 Hz; aromatic), 7.72 (4H, br d, $J \sim$ 7 Hz; aromatic), 7.58 (1H, br t, J = 7.5 Hz; aromatic), 7.50–7.40 (8H, br m; aromatic), 7.20–7.10 (10H, br m; aromatic), 5.76 (1H, br t, $J \sim$ 4 Hz; H-2), 4.47 (1H, br d, $J \sim$ 2.5 Hz; H-4), 4.40 (1H, br s; OH), 4.10–4.00 (2H, m; H-1/H-1′), 3.91 (1H, dd, J = 11.2, 3.3 Hz; H-7), 3.83 (1H, m; H-7′), 3.82 (2H, d, J = 13.2 Hz, *N*-benzyl CH_2), 3.70 (1H, dd, J = 8.8, 2.7 Hz; H-5), 3.63 (2H, d, J = 13.2 Hz, *N*-benzyl CH_2), 3.16 (1H, br td, J = 8.8, 3.3 Hz; H-6), 1.16 (9H, s; Me_3CSi), 0.80 (9H, s; Me_3CSi), 0.75 (9H, s; Me_3CSi), 0.00 (3H, s; *Me*Si), −0.04 (3H, s; *Me*Si), −0.06 (3H, s; *Me*Si), −0.27 (3H, s; *Me*Si); ^{13}C NMR (125 MHz) δ 205.0, 165.2, 139.3 (×2), 133.1 (×2), 129.9, 19.2, 18.2, 18.1 (quat C), 136.0 (×2), 135.9 (×2), 130.0 (×3), 129.8, 129.2 (×4), 128.4 (×4), 128.3 (×3), 127.7 (×4), 127.1 (×2), 79.3, 78.5, 68.8, 60.8 (CH), 62.5, 62.3, 54.8 (×2) (CH_2), 27.2 (×3, Me_3CSi), 25.8 (×3, Me_3CSi), 25.7 (×3, Me_3CSi), −4.8 (*Me*Si), −4.9 (*Me*Si), −5.4 (×2) (*Me*Si); HR FABMS m/z 960.5054 (M + H^+). Calcd for $C_{56}H_{78}NO_7Si_3$, 960.5087.

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