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Stereoselective titanium-mediated aldol reactions of α-benzyloxy methyl ketones

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ABSTRACT

Good levels of 1,4-*anti* asymmetric induction are obtained in the $TiCl_3$(*i*-PrO)-mediated aldol reaction of chiral α-benzyloxy methyl ketones with a wide array of aldehydes. This methodology represents a new approach to substrate-controlled acetate aldol reactions capable of providing highly functionalized fragments in a straightforward manner, which may be useful in the design of more efficient syntheses.

1. Introduction

The development of highly stereoselective aldol methods and their successful application to the synthesis of structurally complex natural products has placed the aldol reaction among the most important carbon–carbon bond-forming processes.[1,2] Nevertheless, the solutions to some issues, such as stereocontrol in *acetate* aldol reactions,[3] remain elusive. It is certainly true that recent advances in catalytic asymmetric-based[4] and chiral auxiliary-based[1,5] approaches provide excellent levels of stereocontrol for a remarkable range of *acetate* aldol reactions, but these are still unable to facilitate the coupling of elaborate fragments in advanced steps of the synthesis of complex natural products.[6] Indeed, such transformations usually require highly reactive species capable of overcoming opposing trends due to the reacting partners, so they are commonly carried out using Mukaiyama[7] or metal enolate-mediated aldol variants.[8,9] In particular, substrate-controlled aldol reactions based on metal enolates from chiral methyl ketones represent an appealing alternative to accomplish such challenging transformations provided that thorough knowledge of the asymmetric induction imparted by the enolate and the aldehyde is available.[9,10] Unfortunately, metal enolate-mediated *acetate* aldol reactions can proceed through several six-membered cyclic transition states of similar energy and both stereocontrol and prediction of the configuration of the new stereocenter become much more difficult than in related aldol reactions from ethyl ketones.[11]

In this context, we have unravelled the complex structure of titanium(IV) enolates of chiral α-alkoxy ketones[12] and have clearly established the crucial influence of titanium Lewis acid on the stereochemical outcome of their aldol reactions. Thus, lactate-derived α-benzyloxy ethyl ketone affords 2,4-*syn*-4,5-*syn* or 2,4-*anti*-4,5-*syn* aldol adducts depending on the stoichiometry and the titanium(IV) Lewis acid employed in the enolization step (Eq. 1 in Scheme 1).[13,14] Keeping in mind such precedents, we envisaged that related α-alkoxy methyl ketones might also furnish 1,4-*syn* or 1,4-*anti* aldol adducts in a straightforward and stereoselective manner (Eq. 2 in Scheme 1).[15,16] Herein, we report our findings for the substrate-controlled titanium-mediated aldol reactions of chiral α-benzyloxy methyl ketones, which prove that the appropriate choice of the titanium(IV) Lewis acid affords 1,4-*anti* aldol adducts in moderate to high diastereoselectivity, and provide valuable knowledge for devising more efficient syntheses of complex natural products.

2. Results and discussion

2.1. Preliminary results

Initially, we chose lactate-derived α-alkoxy methyl ketones **1** and **2** as models to assess the feasibility of the proposed *acetate* aldol reaction and, later on, related α-benzyloxy methyl ketones **3**–**5** were prepared in order to test the scope of such substrate-controlled titanium-mediated aldol reactions (Fig. 1).[17]

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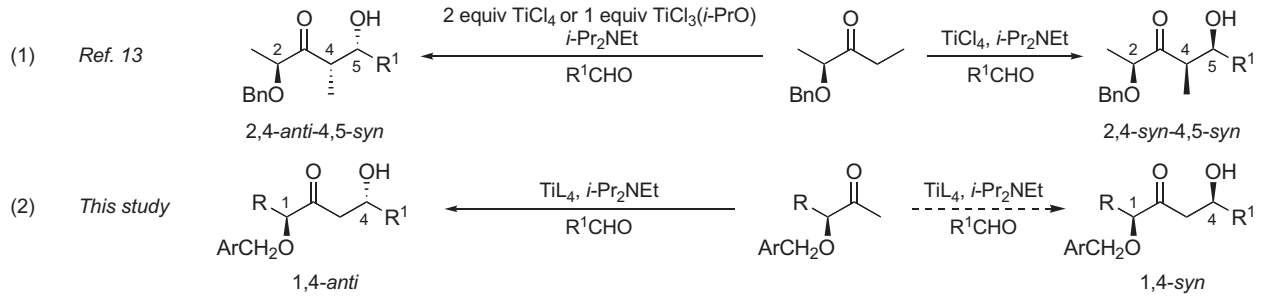


Scheme 1. Titanium-mediated aldol reaction of chiral α-benzyloxy ketones.

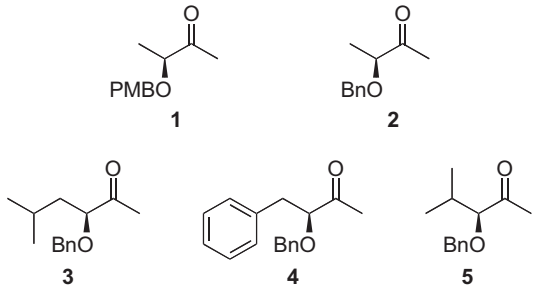


Fig. 1. Chiral α-benzyloxy methyl ketones.

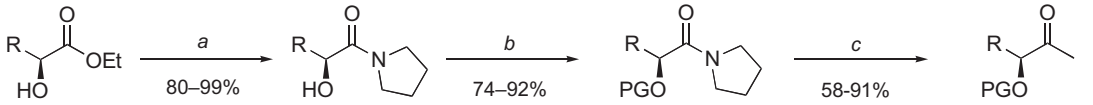
Methyl ketones **1**–**5** were easily prepared in an enantiomerically pure form through acylation of methyl organometallic reagents (MeM, M=Li, MgBr) with *N*-acyl pyrrolidines **6**–**9** derived from the corresponding α-hydroxy esters (Scheme 2).[17] Remarkably, simple stirring of α-hydroxy esters and pyrrolidine in a solvent free process allowed the formation of hydroxy amides **6**–**9**, which were used in the next step without further purification. Then, benzylation under basic conditions gave the resulting benzyloxy amides **10**–**14**, whose treatment with MeM (M=Li, MgBr) provided the desired ketones **1**–**5** in good overall yields (39–66%). Eventually, (*R*)-3-benzyloxy-2-butanone (*ent*-**2**) was likewise obtained from the commercially available (*R*) isobutyl lactate.

With a straightforward and reliable multigram supply of the required methyl ketones to hand, we first evaluated the influence of the enolization conditions on the titanium-mediated aldol reaction of model ketones **1** and **2** with isobutyraldehyde (**a**). The results are summarized in Table 1. Taking advantage of our own experience in the titanium-mediated aldol reaction of α-hydroxy ketones,[13] we initially carried out the enolization of **1** with several titanium Lewis acids (1.1 equiv) and *i*-Pr_2NEt (1.1 equiv) for 1.5 h at −78 °C and the resulting enolate was allowed to react with isobutyraldehyde (**a**, 1.5 equiv) for 0.5 h at the same temperature (see entries 1–4 in Table 1). As expected, the stereochemical outcome of these reactions was highly dependent on the titanium Lewis acid used, but on this occasion the major diastereomer obtained across all the optimization experiments was *anti* adduct **15a** (Table 1). Remarkably, the strength of the titanium Lewis acid was found to be important. As expected, parent titanium(IV) Lewis acid, namely $TiCl_4$, was unsuitable for our purposes because it produced a partial removal of the PMB protecting group. Instead, $TiCl_3$(*i*-PrO) afforded **15a** in a high diastereomeric ratio and yield (dr 86:14, 80% yield, see entry 1), whereas the softer $TiCl_2$(*i*-PrO)$_2$ displayed reduced stereocontrol but an excellent yield (dr 70:30, 90% yield, see entry 2). Moreover, the bulkiness of alkoxy ligands had a minor effect, as the less bulky $TiCl_3$(*n*-PrO) afforded a slightly lower diastereoselectivity and a similar yield (compare entries 1 and 3). Further optimization of the experimental conditions revealed that the enolization step was fairly fast and could be reduced to 0.5 h, and that the amount of aldehyde could safely be reduced to 1.2 equiv without reducing the yield (see entry 4).

Having established the feasibility of the process, we turned our attention to the more robust Bn-protected ketone **2** (see entries 5–9 in Table 1). Almost no diastereoselectivity was observed with $TiCl_4$ (see entries 5 and 6), but better levels of stereocontrol were achieved either with 2.1 equiv of $TiCl_4$ (see entry 7) or softer Lewis acids, such as $TiCl_3$(*i*-PrO) or $TiCl_2$(*i*-PrO)$_2$ (see entries 8 and 9). Indeed, as had been previously observed for PMB-protected ketone **1**, the best diastereoselection in the titanium-mediated aldol reaction of **2** was achieved with $TiCl_3$(*i*-PrO), likewise in comparable yields (compare entries 4 and 8 in Table 1).

2.2. Scope of the $TiCl_3$(*i*-PrO)-mediated aldol reactions of lactate-derived ketones 1 and 2

Next, these experimentally simple conditions were applied to other aliphatic, aromatic and α,β-unsaturated aldehydes. The results are summarized in Table 2 and prove that the lactate-derived methyl ketone **1** affords *anti* aldol adducts **15** from aldehydes **a**–**f** in good yields and diastereomeric ratios (see entries 1–6). Significantly, diastereoselectivity for aliphatic aldehydes was not seriously affected by steric bulk (compare entries 1–4), ranging from dr 86:14 for isobutyraldehyde (**a**) to dr 82:18 for 3-phenylpropanal (**c**). Benzaldehyde (**e**) provided similar results, but both the diastereomeric ratio and the yield dropped for α,β-unsaturated methacrolein (**f**), which afforded *anti* adduct **15f** in dr 75:25 and



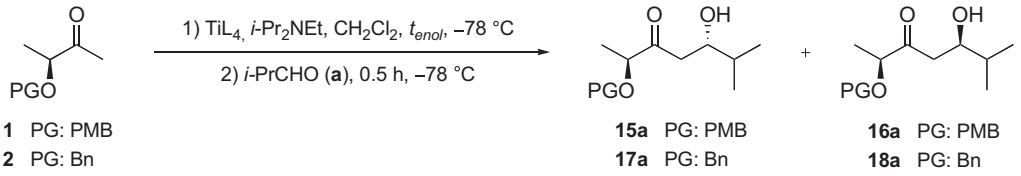
6 R: Me
7 R: *i*-Bu
8 R: Bn
9 R: *i*-Pr

10 PG: PMB, R: Me
11 PG: Bn, R: Me
12 PG: Bn, R: *i*-Bu
13 PG: Bn, R: Bn
14 PG: Bn, R: *i*-Pr

1 PG: PMB, R: Me
2 PG: Bn, R: Me
3 PG: Bn, R: *i*-Bu
4 PG: Bn, R: Bn
5 PG: Bn, R: *i*-Pr

Scheme 2. Reagents and conditions: (a) pyrrolidine, rt (R: Me, *i*-Bu, Bn) or 45 °C (R: *i*-Pr). (b) $ArCH_2Cl$, NaOH, [Oct_3NMe]Cl, toluene (R: Me) or CH_2Cl_2 (R: Bn, *i*-Bu, *i*-Pr), rt. (c) MeLi, THF, −78 °C (R: Me, Bn) or MeMgBr, THF, 0 °C (R: *i*-Bu, *i*-Pr).

Table 1
Titanium-mediated aldol reaction of ketones **1** and **2** with isobutyraldehyde



1 PG: PMB
2 PG: Bn

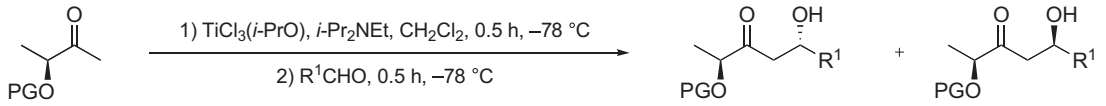
15a PG: PMB
17a PG: Bn

16a PG: PMB
18a PG: Bn

Entry	Ketone	TiL_4 (equiv)	t_{enol} (h)	dr[a] (**15a**:**16a**)	dr[a] (**17a**:**18a**)	Yield[b] (%)
1[c]	**1**	$TiCl_3$(*i*-PrO) (1.1)	1.5	86:14		80
2[c]	**1**	$TiCl_2$(*i*-PrO)$_2$ (1.1)	1.5	70:30		90
3[c]	**1**	$TiCl_3$(*n*-PrO) (1.1)	1.5	83:17		71
4	**1**	$TiCl_3$(*i*-PrO) (1.1)	0.5	86:14		80
5	**2**	$TiCl_4$ (1.1)	0.5		57:43	90
6	**2**	$TiCl_4$ (1.1)+THF (1.1)	0.5		51:49	71
7	**2**	$TiCl_4$ (2.1)	0.5		71:29	77
8	**2**	$TiCl_3$(*i*-PrO) (1.1)	0.5		85:15[d]	80
9	**2**	$TiCl_2$(*i*-PrO)$_2$ (1.1)	0.5		73:27	80

[a] Determined by ^{1}H NMR analysis of the reaction mixture.
[b] Isolated yield of the aldol mixture.
[c] Aldehyde (1.5 equiv) were used.
[d] Determined by HPLC.

Table 2
$TiCl_3$(*i*-PrO)-mediated aldol reactions of ketones **1** and **2**



1 PG: PMB
2 PG: Bn

15 PG: PMB
17 PG: Bn

16 PG: PMB
18 PG: Bn

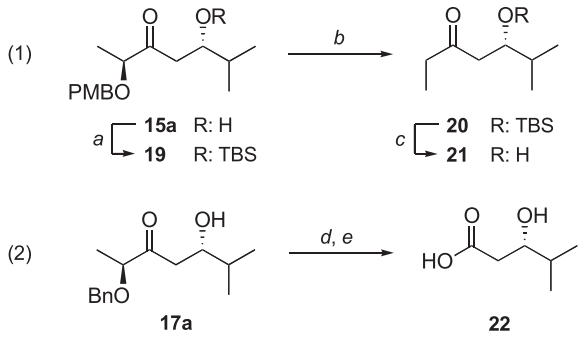
Entry	Ketone	Aldehyde	R^1	dr[a] (**15**:**16**)	dr[a] (**17**:**18**)	Yield[b] (%)
1	**1**	**a**	*i*-Pr	86:14		80
2	**1**	**b**	*i*-Bu	83:17		81
3	**1**	**c**	$Ph(CH_2)_2$	82:18		72
4	**1**	**d**	Et	86:14		70
5	**1**	**e**	Ph	82:18		70
6[c]	**1**	**f**	$H_2C{=}C(CH_3)$	75:25		65
7	**2**	**g**	*t*-Bu		93:7	72
8	**2**	**a**	*i*-Pr		85:15[d]	80
9	**2**	**b**	*i*-Bu		85:15	76
10	**2**	**h**	Pr		80:20	67
11	**2**	**e**	Ph		83:17	66
12[e]	**2**	**i**	4-NO_2–Ph		74:26	67
13	**2**	**j**	4-MeO–Ph		73:27	68
14[e]	**2**	**k**	4-Br–Ph		75:25	67
15[c]	**2**	**f**	$H_2C{=}C(CH_3)$		69:31	58
16[c]	**2**	**l**	(*E*) $CH_3CH{=}CH$		55:45	56

[a] Determined by ^{1}H NMR analysis of the reaction mixture.
[b] Isolated yield of the aldol mixture.
[c] The aldehyde was not distilled.
[d] Determined by HPLC.
[e] A solution of aldehyde in CH_2Cl_2 (1.0 mL) was added via cannula (0.5 mL rinse) to the solution of enolate in CH_2Cl_2 (3.5 mL).

a 65% yield (compare entries 5 and 6). In the same way, the stereocontrol achieved from Bn-protected ketone **2** was highly dependent on the aldehyde partner (see entries 7–16 in Table 2). Indeed, the steric bulk of aliphatic aldehydes affected the diastereoselectivity of these transformations (compare entries 7–10), the best diastereomeric ratio (dr 93:7, entry 7) being provided by pivalaldehyde (**g**). Moreover, ketone **2** afforded comparable stereocontrol with benzaldehyde (**e**), but it was eroded when either electron-withdrawing or electron-donating substituents were present in the aromatic ring (see entries 12–14). Finally, α,β-unsaturated aldehydes offered the poorest diastereoselection (see entries 15 and 16), which was almost non-existent in the case of *E*-crotonaldehyde (**l**).

The absolute stereochemistry of the major diastereomer was secured through analysis of the spectroscopic data for **17e**[10c] and chemical correlation for aldols **15a** and **17a** (Scheme 3). Our previous experience in the removal of the α-OTBS functionality in similar aldol adducts[18] prompted us to test the same strategy for the chemical correlation of **15a**. This involved a three-step sequence in which SmI_2-mediated reductive elimination of the α-OPMB group was the key step (Eq. 1 in Scheme 3). Thus, TBS-protection of **15a** furnished **19**, which was subsequently treated with SmI_2 to provide ethyl ketone **20**.[19] Finally, TBS deprotection afforded (*S*)-5-hydroxy-6-methylheptan-3-one (**21** in Scheme 3) in a 44% overall yield.

Moreover, **17a** was converted into the corresponding β-hydroxy carboxylic acid **22** (Eq. 2 in Scheme 3). Hence, hydrogenolysis of the



Scheme 3. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 71%. (b) SmI_2, 2:1 THF/MeOH, 0 °C, 89%. (c) HF, CH_3CN, rt, 70%. (d) H_2, Pd/C, EtOH, rt. (e) $NaIO_4$, 2:1 MeOH/H_2O, rt; 50% over two steps.

benzyl ether followed by oxidative cleavage of the resulting dihydroxy ketone afforded (*S*)-3-hydroxy-4-methylpentanoic acid (**22** in Scheme 3) in a 50% overall yield. Spectroscopic and physical data for **21** and **22** matched those previously reported in the literature and confirmed the configuration assigned to aldols **15a** and **17a**.[20]

2.3. $TiCl_3$(*i*-PrO)-mediated aldol reactions of ketones 3–5

Having established the generality of the aldol methodology based on lactate-derived ketones, we examined the stereocontrol imparted by other α-benzyloxy methyl ketones. In particular, we studied the aldol reaction of ketones **3**–**5**, containing different R chains (R: *i*-Bu, Bn and *i*-Pr, respectively, see Fig. 1), with some representative aldehydes, such as isobutyraldehyde (**a**), benzaldehyde (**e**) and methacrolein (**f**). The results are summarized in Table 3.

These results reveal that the titanium aldol chemistry optimized for lactate-derived ketones can be expanded to other α-benzyloxy methyl ketones with some caution. Indeed, the data summarized in Tables 2 and 3 show that yields from ketones **3**–**5** are always much better than those obtained from **1** and **2** while changes in diastereoselectivity do not seem to follow any pattern. For instance, isobutyraldehyde (**a**) participates in highly diastereoselective aldol reactions with ketones **2**–**4** (dr 85:15), but a significant loss of stereocontrol is observed for bulky ketone **5** (dr 67:33). In turn, the best results for benzaldehyde (**e**) are obtained with bulky ketones **4** and **5**, whereas the worst diastereomeric ratios for conjugated methacrolein (**f**) are achieved both with the least and the most bulky ketones, **2** and **5**, respectively. From a general point of view, these results prove that such *acetate* aldol reactions consistently afford the 1,4-*anti* adduct, but the availability of various transition states prevents prediction of the diastereoselectivity of a particular reaction.

2.4. Double asymmetric aldol reactions

Although a simple theoretical model for these transformations is still elusive, the aforementioned results prove that the titanium-mediated aldol reaction of α-benzyloxy methyl ketones can be useful for the stereoselective construction of β-hydroxy carbonyl subunits in advanced steps of a synthesis. Therefore, considering that these reactions usually involve chiral aldehydes, we next assessed the ability of lactate-derived ketones **1** and **2** to govern the stereochemical outcome in double asymmetric processes[21] with model chiral β- and α-hydroxy aldehydes, such as **29**[22] and **30**[23] (Fig. 2).

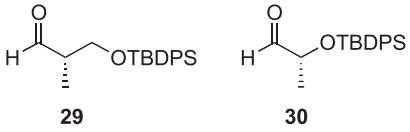
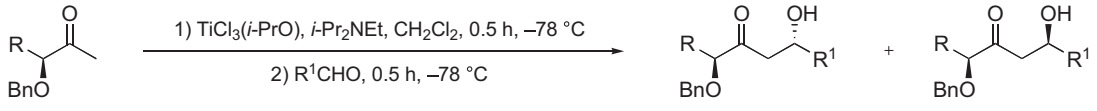


Fig. 2. Chiral β- and α-hydroxy aldehydes.

Conventional wisdom accepts that nucleophilic additions to chiral α-methyl aldehydes without other chelating functional groups usually render the corresponding Felkin adduct.[1,2,9,24] Thus, it was not surprising to observe that matched pairs involving ketones **1** and **2** with aldehyde **29** afforded the corresponding Felkin adducts **31** and **33** in excellent diastereoselectivities (Scheme 4), whereas enantiomeric ketone *ent*-**2** overcame the stereochemical bias imparted by aldehyde **29** and afforded an 80:20 mixture of diastereomers (**35** and **36**) in an 81% yield.

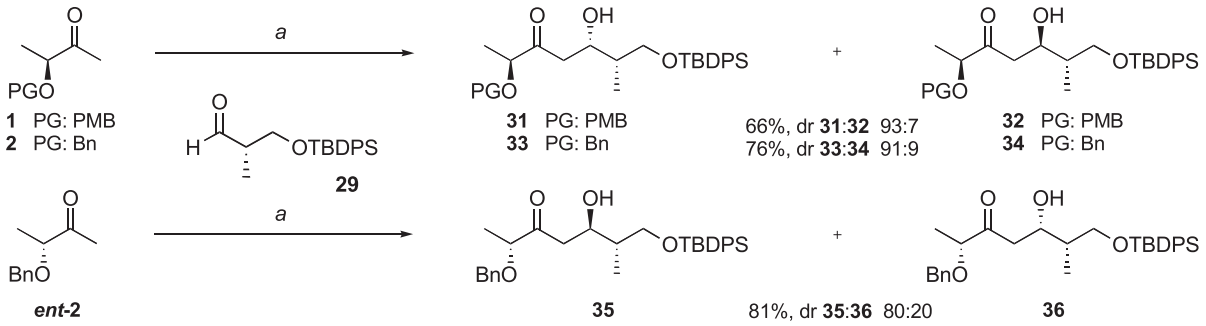
Likewise, double asymmetric processes with chiral α-hydroxy aldehydes were next addressed. Pioneering studies by Heathcock on the aldol additions of achiral and chiral α-hydroxy methyl and ethyl ketones to α-hydroxy aldehydes early proved the Cornforth-like stereochemical induction of these aldehydes.[25,26] More recently, this trend has been definitely established by Evans in a comprehensive study on the aldol reaction of methyl ketones with α-hydroxy aldehydes.[27,28] Thus, we anticipated that the aldol additions of ketones **1** and **2** to chiral aldehydes **30** and *ent*-**30** containing an oxygenated Cα stereocenter would proceed with a different diastereoselectivity.

Table 3
$TiCl_3$(*i*-PrO)-mediated aldol reactions of ketones **3**, **4** and **5**



Entry	Ketone	Aldehyde	R^1	Aldols	dr[a]	Yield[b] (%)
1	**3**	**a**	*i*-Pr	**23a**:**24a**	85:15	93
2	**3**	**e**	Ph	**23e**:**24e**	75:25	94
3[c]	**3**	**f**	$H_2C{=}C(CH_3)$	**23f**:**24f**	81:19	85
4	**4**	**a**	*i*-Pr	**25a**:**26a**	85:15	92
5	**4**	**e**	Ph	**25e**:**26e**	88:12	96
6[c]	**4**	**f**	$H_2C{=}C(CH_3)$	**25f**:**26f**	83:17	78
7	**5**	**a**	*i*-Pr	**27a**:**28a**	67:33	90
8	**5**	**e**	Ph	**27e**:**28e**	87:13	97
9[c]	**5**	**f**	$H_2C{=}C(CH_3)$	**27f**:**28f**	64:36	80

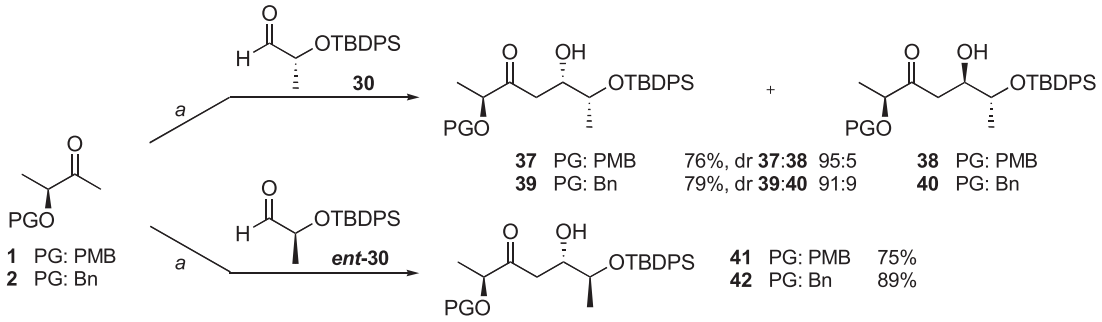
[a] Determined by ^1H NMR analysis of the reaction mixture.
[b] Isolated yield of the aldol mixture.
[c] The aldehyde was not distilled.



Scheme 4. Reagents and conditions: (a) (i) $TiCl_3(i\text{-PrO})$, $i\text{-Pr}_2NEt$, CH_2Cl_2, −78 °C; (ii) **29**, −78 °C.

According to the Cornforth model, reactions of ketones **1** and **2** with aldehyde **30** gave aldol adducts **37** and **39** in high diastereomeric ratios (Scheme 5). Nevertheless, we were completely taken aback when the aldol reaction of either ketone **1** or **2** with

Having demonstrated that the titanium-mediated aldol reactions of chiral α-benzyloxy methyl ketones proceed in a highly stereoselective manner in double asymmetric processes, we next explored the conversion of the ensuing adducts into arrays

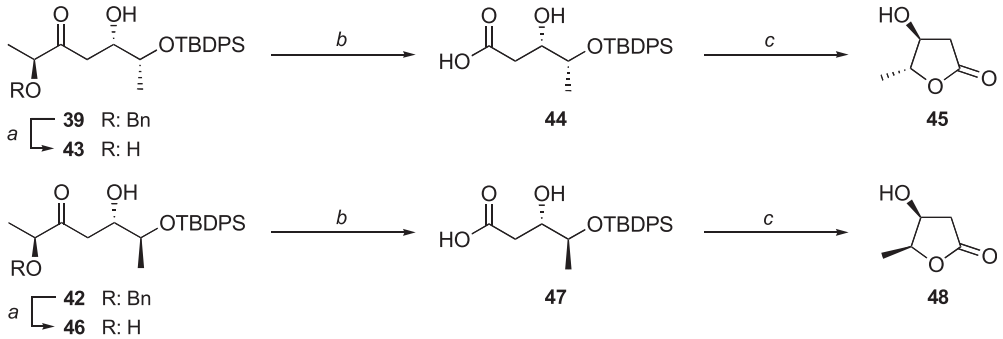


Scheme 5. Reagents and conditions: (a) (i) $TiCl_3(i\text{-PrO})$, $i\text{-Pr}_2NEt$, CH_2Cl_2, −78 °C; (ii) **30** or *ent*-**30**, −78 °C.

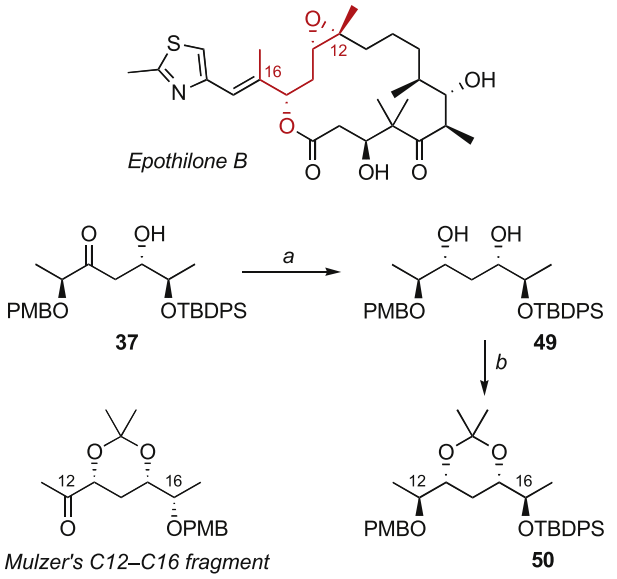
ent-**30** furnished a single diastereomer (**41** and **42**, respectively) in remarkable yields (Scheme 5). Thus, the diastereoselectivity achieved in both reactions represented in Scheme 5 was astonishingly high and the anti-Cornforth adducts **41** and **42** were even more favoured than their Cornforth counterparts **37** and **39**.[29] Faced with such a puzzling result, a verification of the stereochemistry was considered inavoidable. Hence, the configuration of aldols **39** and **42** was firmly established through the sequential removal of protecting groups to obtain the corresponding lactones (Scheme 6). Hydrogenolysis of the benzyl ether followed by oxidative cleavage of the resulting dihydroxy ketone afforded β-hydroxy acids **44** and **47**, respectively. Then, TBDPS deprotection gave lactones **45** and **48** in good overall yields. Their spectroscopic and physical data matched those previously reported in the literature[30,31] and confirmed the configuration assigned to aldols **39** and **42**.

embedded in the structure of natural products. Our target was the C12–C16 fragment of epothilone B (Scheme 7),[32] the synthesis of which had already been addressed by Mulzer several years ago.[33]

In fact, any structure having the same carbon backbone with the desired configuration at C13 and C15 stereocenters would serve as a synthetic analogue of Mulzer's C12–C16 fragment. So, provided that the aldol reaction of ketone **1** with aldehyde **30** had delivered adduct **37** diastereoselectively (dr 95:5) in a high yield (see Scheme 5), we envisaged that it could lead to the desired C12–C16 fragment in a straightforward manner. Hence, stereoselective *syn* reduction of β-hydroxy ketone **37** under Kiyooka conditions[34] afforded the desired *syn* diol **49** (dr 88:12), which was isolated as a single diastereomer in a 78% yield after purification. Finally, protection of the diol as isopropylidene acetal under standard conditions delivered **50** in an 82% yield.[35] Therefore, a stereoselective



Scheme 6. Reagents and conditions: (a) H_2, Pd/C, EtOH, rt. (b) $NaIO_4$, 2:1 $MeOH/H_2O$, rt. (c) HF, CH_3CN, rt; 40% overall yield for **45**, 50% overall yield for **48**.



Scheme 7. Reagents and conditions: (a) DIBALH, THF, −78 °C; 78%. (b) 1:1 $Me_2C(OMe)_2/CH_2Cl_2$, cat PPTS, rt, 82%.

synthesis of the C12–C16 fragment of epothilone B was accomplished in three steps in a 48% overall yield starting from ketone **1**. This example demonstrates that our substrate-controlled aldol reaction methodology based on chiral α-benzyloxy methyl ketones is a useful tool for the synthesis of natural products.

3. Conclusions

In summary, the titanium-mediated aldol reaction of chiral α-benzyloxy methyl ketones is highly sensitive to the titanium Lewis acid used in the enolization step. High yields and a remarkable 1,4-*anti* induction have been obtained for aliphatic and aromatic aldehydes when the reaction is carried out with $TiCl_3$(*i*-PrO). Moreover, high diastereoselectivities have been achieved in double asymmetric processes with chiral α- and β-oxygenated aldehydes and an example of application in the synthesis of the C12–C16 fragment of epothilone B has been described. Thus, the titanium-based methodology reported here represents a new approach to the substrate-controlled acetate aldol reaction, which may be helpful to design more efficient syntheses.

4. Experimental section

4.1. General information

Unless otherwise noted, all oxygen and moisture-sensitive reactions were conducted in oven-dried glassware under a N_2 atmosphere with anhydrous solvents. The solvents and reagents were dried and purified when necessary according to standard procedures. All commercial reagents were used as received. Melting points were determined with a Gallenkamp apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} plates and analyzed by UV (254 nm) and stained with *p*-anisaldehyde or phosphomolybdic acid; R_f values are approximate. Flash Column chromatographies were performed on SDS silica gel 60 (35–70 μm). High-pressure liquid chromatography (HPLC) analyses were performed under isocratic conditions with a Tracer Spherisorb S3 W column with a 0.9 mL min^{-1} flow at rt; the eluent and the retention time are specified for each case. Specific rotations ($[\alpha]_D$) were determined at 20 °C on a Perkin–Elmer 241 MC polarimeter. IR spectra were recorded on a Nicolet 6700 FT-IR Thermo Scientific spectrometer and only the more representative frequencies (ν) are reported. ^{1}H NMR (500, 400 or 300 MHz) and ^{13}C NMR (100.6 or 75.4 MHz) spectra were recorded on Varian spectrometers. Chemical shifts (δ) are quoted in parts per million and referenced to internal TMS (δ 0.00 for ^{1}H NMR), DMSO-d_6 (δ 2.50 for ^{1}H NMR and 39.5 for ^{13}C NMR) or $CDCl_3$ (δ 77.0 for ^{13}C NMR); coupling constants (J) are quoted in Hertz; data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; sept, septuplet; m, multiplet (and their corresponding combinations); where necessary, 2D techniques (NOESY, COSY, HSQC) were also used to assist on structure elucidation. High resolution mass spectra (HRMS) were obtained with an Agilent 1100 spectrometer by the Unitat d'Espectrometria de Masses, Universitat de Barcelona.

4.2. Preparation of methyl ketones 1–5

*4.2.1. (S)-3-(p-Methoxybenzyloxy)-2-butanone (**1**).* A 1.6 M solution of MeLi in Et_2O (3.8 mL, 6.1 mmol) was added dropwise to a solution of **10** (1.58 g, 6.0 mmol) in THF (60 mL) at −78 °C under N_2. The resulting mixture was stirred for 5 min at −78 °C, quenched by addition of satd NH_4Cl (10 mL), and vigorously stirred at rt for 10 min. The mixture was diluted with Et_2O and the organic layer was washed with satd NH_4Cl, brine, dried ($MgSO_4$) and concentrated. The resulting oil was purified by column chromatography (90:10 hexanes/EtOAc) to afford 1.12 g (89% yield) of **1** as a colourless oil. R_f (90:10 hexanes/EtOAc) 0.20. $[\alpha]_D^{20}$ −35.5 (*c* 4.5, $CHCl_3$) [lit.[10a] *ent*-**1** $[\alpha]_D^{20}$ +33.1 (*c* 4.11, $CHCl_3$)]. IR (film) ν 2934, 2838, 1717, 1613, 1515, 1250, 1175, 1111, 1034 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.24 (2H, m, Ar*H*), 6.91–6.86 (2H, m, Ar*H*), 4.49 (1H, d, *J*=11.3, PhC*H*$_x$H$_y$), 4.42 (1H, d, *J*=11.3, PhCH$_x$*H*$_y$), 3.88 (1H, q, *J*=6.9, *CH*OPMB), 3.80 (3H, s, *Me*O), 2.18 (3H, s, CO*Me*), 1.32 (3H, d, *J*=6.9, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 211.3, 159.4, 129.6, 129.4, 113.9, 80.5, 71.5, 55.2, 24.9, 17.2. HRMS (+FAB): MH^+, found 209.1178, $C_{12}H_{17}O_3$ requires 209.1178.

*4.2.2. (S)-3-Benzyloxy-2-butanone (**2**).* The abovementioned experimental procedure was applied to **11** (1.64 g, 7.0 mmol) to afford 898 mg (72% yield) of **2** as a colourless oil. R_f (85:15 hexanes/EtOAc) 0.30. $[\alpha]_D^{20}$ −38.7 (*c* 1.0, $CHCl_3$) [lit.[10c] $[\alpha]_D^{24}$ −35.2 (*c* 2.51, $CHCl_3$)]. IR (film) ν 3031, 2982, 2868, 1718, 1497, 1454, 1355, 1116, 1065 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m, Ar*H*), 4.59 (1H, d, *J* =11.7, PhC*H*$_x$H$_y$), 4.49 (1H, d, *J*=11.7, PhCH$_x$*H*$_y$), 3.91 (1H, q, *J*=6.9, *CH*OBn), 2.20 (3H, s, CO*Me*), 1.35 (3H, d, *J*=6.9, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 211.2, 137.5, 128.5, 127.9, 127.7, 80.8, 71.8, 25.0, 17.2. HRMS (+ESI): MNa^+, found 201.0894, $C_{11}H_{14}NaO_2$ requires 201.0886.

*4.2.3. (S)-3-Benzyloxy-5-methyl-2-hexanone (**3**).* A 1.4 M solution of MeMgBr in 75:25 toluene/THF (5.7 mL, 8.0 mmol) was added dropwise to a solution of **12** (1.11 g, 4.0 mmol) in THF (40 mL) at 0 °C under N_2. The resulting mixture was stirred for 30 min at 0 °C, then quenched and worked-up as in the previous case to afford 889 mg (91% yield) of **3** as a colourless oil. R_f (85:15 hexanes/EtOAc) 0.35. $[\alpha]_D^{20}$ −79.9 (*c* 1.0, $CHCl_3$) [lit.[36] *ent*-**3** $[\alpha]_D^{20}$ +83 (*c* 1.0, $CHCl_3$, 96% *ee*)]. IR (film) ν 3025, 2952, 2927, 2862, 1712, 1450, 1348, 1124, 1091 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.24 (5H, m, Ar*H*), 4.58 (1H, d, *J*=11.8, PhC*H*$_x$H$_y$), 4.39 (1H, d, *J*=11.8, PhCH$_x$*H*$_y$), 3.81 (1H, dd, *J*=9.5, 4.2, *CH*OBn), 2.18 (3H, s, CO*Me*), 1.89–1.75 (1H, m, *CH*Me$_2$), 1.64 (1H, ddd, *J*=13.9, 9.5, 5.2, C*H*$_x$H$_y$CHMe$_2$), 1.35 (1H, ddd, *J*=13.9, 8.8, 4.2, CH$_x$*H*$_y$CHMe$_2$), 0.92 (3H, d, *J*=6.8, CH*Me*), 0.85 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.9, 137.4, 128.5, 128.0, 83.8, 72.5, 41.0, 24.9, 24.5, 23.2, 21.7. HRMS (+ESI): MNa^+, found 243.1362, $C_{14}H_{20}NaO_2$ requires 243.1355.

*4.2.4. (S)-3-Benzyloxy-4-phenyl-2-butanone (**4**).* Experimental procedure described for **1** was applied to **13** (1.90 g, 6.0 mmol) with

a reaction time of 30 min to afford 902 mg (58% yield) of **4** as a colourless oil. R_f (70:30 hexanes/EtOAc) 0.40. $[\alpha]_D^{20}$ −60.8 (*c* 1.0, $CHCl_3$). IR (film) ν 3086, 3063, 3024, 2919, 2864, 1713, 1495, 1453, 1352, 1099 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.12 (10H, m, Ar*H*), 4.52 (1H, d, *J*=11.7, PhCH_xH_yO), 4.36 (1H, d, *J*=11.7, PhCH_xH_yO), 3.99 (1H, dd, *J*=8.1, 4.8, C*H*OBn), 3.01 (1H, dd, *J*=14.1, 4.8, PhCH_xH_y), 2.93 (1H, dd, *J*=14.1, 8.1, PhCH_xH_y), 2.13 (3H, s, CO*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 210.8, 137.3, 137.0, 129.5, 128.4, 127.8, 127.7, 126.7, 85.9, 72.6, 38.5, 26.0. HRMS (+ESI): MNa^+, found 277.1204, $C_{17}H_{18}NaO_2$ requires 277.1199.

*4.2.5. (S)-3-Benzyloxy-4-methyl-2-pentanone (**5**).* The experimental procedure described for **3** was applied to **14** (1.30 g, 5.0 mmol) to afford 722 mg (71% yield) of **5** as a colourless oil. R_f (85:15 hexanes/EtOAc) 0.35. $[\alpha]_D^{20}$ −88.4 (*c* 1.0, $CHCl_3$). IR (film) ν 3030, 2960, 2870, 1710, 1455, 1351, 1090, 1073 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.24 (5H, m, Ar*H*), 4.58 (1H, d, *J*=11.7, PhCH_xH_y), 4.39 (1H, d, *J*=11.7, PhCH_xH_y), 3.43 (1H, d, *J*=6.6, C*H*OBn), 2.16 (3H, s, CO*Me*), 2.10–1.91 (1H, m, C*H*Me_2), 0.99 (3H, d, *J*=6.6, CH*Me*), 0.91 (3H, d, *J*=6.9, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 211.7, 137.6, 128.4, 127.9, 127.8, 90.6, 72.9, 30.9, 25.8, 18.7, 18.1. HRMS (+ESI): MNa^+, found 229.1202, $C_{13}H_{18}NaO_2$ requires 229.1199.

4.3. General procedure for the $TiCl_3$(*i*-PrO)-mediated aldol reaction

Freshly distilled Ti(*i*-PrO)$_4$ (80 μL, 0.27 mmol) was added dropwise to a solution of $TiCl_4$ (90 μL, 0.82 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C under N_2. The resulting white mixture was stirred for 15 min at 0 °C and 10 min at rt. It was diluted with CH_2Cl_2 (1.0 mL), and the resulting colourless solution was added via cannula (2×0.5 mL rinse) to a solution of the ketone (1.0 mmol) in CH_2Cl_2 (2.0 mL) at −78 °C under N_2. The resulting yellow solution was stirred for 5 min and *i*-Pr_2NEt (190 μL, 1.1 mmol) was added dropwise. The resulting dark red solution was stirred for 30 min at −78 °C and after the dropwise addition of the aldehyde (1.2 mmol), stirring was continued for 30 min at −78 °C. The reaction was quenched by addition of satd NH_4Cl (5 mL) and vigorously stirred at rt for 10 min. The mixture was diluted with Et_2O and the organic layer was washed with H_2O, satd $NaHCO_3$, and brine, dried ($MgSO_4$) and concentrated. The reaction crude was analyzed by NMR or HPLC and purified by column chromatography.

*4.3.1. (2S,5S)-5-Hydroxy-2-(p-methoxybenzyloxy)-6-methyl-3-heptanone (**15a**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.30. IR (film) ν 3514 (br), 2961, 1716, 1613, 1514, 1466, 1250, 1111 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (2H, m, Ar*H*), 6.91–6.87 (2H, m, Ar*H*), 4.51 (1H, d, *J*=11.4, PhCH_xH_y), 4.45 (1H, d, *J*=11.4, PhCH_xH_y), 3.91 (1H, q, *J*=6.9, C*H*OPMB), 3.85–3.80 (1H, m, C*H*OH), 3.80 (3H, s, *Me*O), 2.75 (1H, dd, *J*=17.8, 2.4, COCH_xH_y), 2.61 (1H, dd, *J*=17.8, 9.7, COCH_xH_y), 1.75–1.64 (1H, m, C*H*Me_2), 1.33 (3H, d, *J*=6.9, *Me*CHOPMB), 0.94 (3H, d, *J*=6.9, CH*Me*), 0.92 (3H, *J*=6.9, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.5, 159.4, 129.5, 129.4, 113.9, 80.2, 72.1, 71.6, 55.2, 41.1, 33.1, 18.3, 17.7, 17.2. HRMS (+FAB): MH^+, found 281.1747, $C_{16}H_{25}O_4$ requires 281.1753.

Minor aldol (**16a**). ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (1H, q, *J*=6.9, C*H*OPMB), 2.62 (1H, dd, *J*=17.7, 10.7, COCH_xH_y). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 80.5, 72.2, 71.6, 41.0, 33.2.

*4.3.2. (2S,5S)-2-Benzyloxy-5-hydroxy-6-methyl-3-heptanone (**17a**).* Colourless oil. R_f (75:25 hexanes/EtOAc) 0.25. HPLC (98:2 hexanes/*i*-PrOH) t_R=13.8 min. IR (film) ν 3495 (br), 2957, 2871, 1714, 1454, 1367, 1113, 1053, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (5H, m, Ar*H*), 4.58 (1H, d, *J*=11.6, PhCH_xH_y), 4.52 (1H, d, *J*=11.6, PhCH_xH_y), 3.94 (1H, q, *J*=6.8, C*H*OBn), 3.89–3.75 (1H, m, C*H*OH), 2.86 (1H, br s, CHO*H*), 2.77 (1H, dd, *J*=17.6, 2.4, COCH_xH_y), 2.63 (1H, dd, *J*=17.6, 9.8, COCH_xH_y), 1.77–1.64 (1H, m, C*H*Me_2), 1.35 (3H, d, *J*=6.8, CH*Me*), 0.94 (3H, d, *J*=6.8, CH*Me*), 0.92 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.4, 137.4, 128.5, 128.0, 127.8, 80.6, 72.1, 71.9, 41.2, 33.1, 18.4, 17.7, 17.2. HRMS (+ESI): MNa^+, found 273.1467, $C_{15}H_{22}NaO_3$ requires 273.1461.

Minor aldol (**18a**). HPLC (98:2 hexanes/*i*-PrOH) t_R=14.8 min. ^1H NMR (400 MHz, $CDCl_3$) δ 3.94 (1H, q, *J*=6.8, C*H*OBn), 2.70 (1H, dd, *J*=17.6, 3.6, COCH_xH_y), 2.64 (1H, dd, *J*=17.6, 8.8, COCH_xH_y), 0.91 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 80.8, 72.2, 71.9, 41.1, 33.2, 17.2.

*4.3.3. (2S,5R)-5-Hydroxy-2-(p-methoxybenzyloxy)-7-methyl-3-octanone (**15b**).* Colourless oil. R_f (70:30 hexanes/EtOAc) 0.25. IR (film) ν 3473 (br), 2956, 1716, 1613, 1514, 1466, 1248, 1036 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.25 (2H, m, Ar*H*), 6.91–6.87 (2H, m, Ar*H*), 4.50 (1H, d, *J*=11.3, ArCH_xH_y), 4.45 (1H, d, *J*=11.3, ArCH_xH_y), 4.16–4.05 (1H, m, C*H*OH), 3.90 (1H, q, *J*=6.8, C*H*OPMB), 3.81 (3H, s, *Me*O), 2.88 (1H, d, *J*=3.3, CHO*H*), 2.76 (1H, dd, *J*=18.0, 2.7, COCH_xH_y), 2.61 (1H, dd, *J*=18.0, 9.0, COCH_xH_y), 1.86–1.73 (1H, m, C*H*Me_2), 1.49 (1H, ddd, *J*=13.7, 9.0, 5.5, CH_xH_yCHMe_2), 1.33 (3H, d, *J*=6.8, *Me*CHOPMB), 1.15 (1H, ddd, *J*=13.7, 8.8, 4.5, CH_xH_yCHMe_2), 0.92 (3H, d, *J*=6.6, CH*Me*), 0.91 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.2, 159.4, 129.6, 129.5, 113.9, 80.2, 71.5, 65.6, 55.2, 45.7, 44.7, 24.3, 23.3, 22.0, 17.1. HRMS (+FAB): MH^+, found 295.1898, $C_{17}H_{27}O_4$ requires 295.1909.

Minor aldol (**16b**). ^1H NMR (400 MHz, $CDCl_3$) δ 2.86 (1H, d, *J*=3.6, CHO*H*), 1.32 (3H, d, *J*=6.9, *Me*CHOPMB), 0.91 (3H, d, *J*=6.7, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 129.4, 80.4, 71.6, 45.5, 44.5, 23.8, 21.6.

*4.3.4. (2S,5R)-5-Hydroxy-2-(p-methoxybenzyloxy)-7-phenyl-3-heptanone (**15c**).* Colourless oil. R_f (75:25 hexanes/EtOAc) 0.20. IR (film) ν 3473 (br), 3032, 2937, 1716, 1612, 1514, 1455, 1302, 1250, 1036 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.12 (7H, m, Ar*H*), 6.89–6.87 (2H, m, Ar*H*), 4.48 (1H, d, *J*=11.2, ArCH_xH_y), 4.44 (1H, d, *J*=11.2, ArCH_xH_y), 4.09–3.98 (1H, m, C*H*OH), 3.88 (1H, q, *J*=6.8, C*H*OPMB), 3.80 (3H, s, *Me*O), 2.85–2.78 (1H, m, CH_xH_yPh), 2.79 (1H, dd, *J*=18.0, 2.6, COCH_xH_y), 2.72–2.65 (1H, m, CH_xH_yPh), 2.64 (1H, dd, *J*=18.0, 9.2, COCH_xH_y), 1.88–1.78 (1H, m, CH_xH_yCH_2Ph), 1.75–1.66 (1H, m, CH_xH_yCH_2Ph), 1.30 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.2, 159.5, 141.8, 129.5, 129.3, 128.4 (×2), 125.8, 113.9, 80.2, 71.6, 66.8, 55.2, 44.2, 38.2, 31.7, 17.1.

Minor aldol (**16c**). ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 80.4, 44.1.

*4.3.5. (2S,5R)-5-Hydroxy-2-(p-methoxybenzyloxy)-3-heptanone (**15d**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.20. IR (film) ν 3488 (br), 2936, 1715, 1612, 1514, 1463, 1249, 1109, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (2H, m, Ar*H*), 6.91–6.87 (2H, m, Ar*H*), 4.50 (1H, d, *J*=11.2, PhCH_xH_y), 4.45 (1H, d, *J*=11.2, PhCH_xH_y), 3.99–3.93 (1H, m, C*H*OH), 3.90 (1H, q, *J*=6.8, C*H*OPMB), 3.81 (3H, s, *Me*O), 2.79 (1H, dd, *J*=18.0, 2.6, COCH_xH_y), 2.61 (1H, dd, *J*=18.0, 9.2, COCH_xH_y), 1.59–1.41 (2H, m, CH_2Me), 1.32 (3H, d, *J*=6.8, CH*Me*), 0.95 (3H, t, *J*=7.4, CH_2*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.2, 159.5, 129.5, 129.4, 113.9, 80.2, 71.5, 68.9, 55.2, 43.7, 29.4, 17.1, 9.8.

Minor aldol (**16d**). ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (1H, q, *J*=6.8, C*H*OPMB), 2.71 (1H, dd, *J*=18.0, 3.2, COCH_xH_y), 0.94 (3H, t, *J*=7.4, CH_2*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.3, 80.4, 71.6, 43.6.

*4.3.6. (1S,4S)-1-Hydroxy-4-(p-methoxybenzyloxy)-1-phenyl-3-pentanone (**15e**).* Colourless oil. R_f (75:25 hexanes/EtOAc) 0.30. IR (film) ν 3475 (br), 3032, 2935, 1717, 1612, 1514, 1454, 1302, 1248, 1033 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (7H, m, Ar*H*), 6.89–6.86 (2H, m, Ar*H*), 5.16 (1H, dd, *J*=7.5, 4.9, C*H*OH), 4.48 (1H, d, *J*=11.3, ArCH_xH_y), 4.42 (1H, d, *J*=11.3, ArCH_xH_y), 3.90 (1H, q, *J*=6.8, C*H*OPMB), 3.80 (3H, s, *Me*O), 3.03–2.92 (2H, m, COCH_2), 1.30 (3H, d,

J=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.3, 159.5, 142.9, 129.6, 129.4, 128.5, 127.7, 125.7, 113.9, 80.2, 71.6, 69.9, 55.3, 46.2, 17.0.

Minor aldol (**16e**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (1H, dd, J=9.2, 3.2, C*H*OH), 3.01 (1H, dd, J=17.6, 9.2, COC*H*$_x$H$_y$), 2.87 (1H, dd, J=17.6, 3.2, COCH$_x$*H*$_y$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 80.4, 71.7, 46.1.

*4.3.7. (2S,5S)-5-Hydroxy-2-(p-methoxybenzyloxy)-6-methyl-6-hepten-3-one (**15f**).* Colourless oil. R_f (75:25 hexanes/EtOAc) 0.30. IR (film) ν 3486 (br), 3074, 2936, 1717, 1612, 1514, 1456, 1302, 1248, 1035 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (2H, m, Ar*H*), 6.91–6.87 (2H, m, Ar*H*), 5.02–5.01 (1H, m, C=C*H*$_x$H$_y$), 4.87–4.86 (1H, m, C=CH$_x$*H*$_y$), 4.51 (1H, d, J=11.2, ArC*H*$_x$H$_y$), 4.46 (1H, d, J=11.2, ArCH$_x$*H*$_y$), 3.92 (1H, q, J=6.8, C*H*OPMB), 3.81–3.78 (1H, m, C*H*OH), 3.80 (3H, s, *Me*O), 2.84–2.77 (2H, m, COC*H*$_2$), 1.74 (3H, br s, *Me*C=CH$_2$), 1.33 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.4, 159.5, 145.8, 129.6, 129.4, 113.9, 111.2, 80.2, 71.6, 70.9, 55.3, 42.8, 18.3, 17.1.

Minor aldol (**16f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (1H, q, J=6.8, C*H*OPMB), 2.71 (1H, dd, J=17.2, 3.2, COC*H*$_x$H$_y$), 1.73 (3H, br s, *Me*C=CH$_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.5, 145.9, 111.1, 80.4, 71.7, 71.0, 42.7.

*4.3.8. (2S,5S)-2-Benzyloxy-5-hydroxy-6,6-dimethyl-3-heptanone (**17g**).* Colourless oil. R_f (75:25 hexanes/EtOAc) 0.25. $[\alpha]_D^{20}$ −60.1 (c 1.2, $CHCl_3$, 86% *de*). IR (film) ν 3518 (br), 2955, 2869, 1715, 1456, 1365, 1113, 1081 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.25 (5H, m, Ar*H*), 4.56 (1H, d, J=11.6, PhC*H*$_x$H$_y$), 4.52 (1H, d, J=11.6, PhCH$_x$*H*$_y$), 3.94 (1H, q, J=6.8, C*H*OBn), 3.73 (1H, ddd, J=10.4, 3.2, 2.0, C*H*OH), 2.78 (1H, d, J=3.2, CHO*H*), 2.77 (1H, dd, J=17.6, 2.0, COC*H*$_x$H$_y$), 2.59 (1H, dd, J=17.6, 10.4, COCH$_x$*H*$_y$), 1.35 (3H, d, J=6.8, CH*Me*), 0.91 (9H, s, C*Me*$_3$). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 214.5, 137.4, 128.5, 128.0, 127.9, 80.7, 74.8, 71.9, 39.2, 34.3, 25.6, 17.2. HRMS (+ESI): MH$^+$, found 265.1801, $C_{16}H_{25}O_3$ requires 265.1798.

Minor aldol (**18g**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (1H, q, J=6.8, C*H*OBn), 2.81 (1H, d, J=3.2, CHO*H*), 2.71 (1H, dd, J=17.6, 2.0, COC*H*$_x$H$_y$), 0.90 (9H, s, C*Me*$_3$). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 74.9, 17.1.

*4.3.9. (2S,5R)-2-Benzyloxy-5-hydroxy-7-methyl-3-octanone (**17b**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.20. IR (film) ν 3470 (br), 2949, 2924, 2861, 1714, 1452, 1110, 1064 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (5H, m, Ar*H*), 4.58 (1H, d, J=11.5, PhC*H*$_x$H$_y$), 4.52 (1H, d, J=11.5, PhCH$_x$*H*$_y$), 4.18–4.08 (1H, m, C*H*OH), 3.92 (1H, q, J=6.8, C*H*OBn), 2.75 (1H, dd, J=18.0, 3.0, COC*H*$_x$H$_y$), 2.61 (1H, dd, J=18.0, 9.0, COCH$_x$*H*$_y$), 1.86–1.74 (1H, m, C*H*Me$_2$), 1.49 (1H, ddd, J=13.7, 9.0, 5.4, C*H*$_x$H$_y$CHMe$_2$), 1.35 (3H, d, J=6.8, CH*Me*), 1.16 (1H, ddd, J=13.7, 8.8, 4.5, CH$_x$*H*$_y$CHMe$_2$), 0.92 (3H, d, J=6.7, CH*Me*), 0.91 (3H, d, J=6.7, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 214.1, 137.4, 128.5, 128.0, 127.8, 80.5, 71.9, 65.6, 45.7, 44.7, 24.4, 23.3, 22.0, 17.1. HRMS (+ESI): MNa$^+$, found 287.1621, $C_{16}H_{24}NaO_3$ requires 287.1617.

Minor aldol (**18b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (1H, q, J=6.8, C*H*OBn), 1.35 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 214.2, 80.8, 44.6.

*4.3.10. (2S,5R)-2-Benzyloxy-5-hydroxy-3-octanone (**17h**).* Colourless oil. R_f (75:25 hexanes/EtOAc) 0.20. IR (film) ν 3453 (br), 2956, 2926, 2866, 1714, 1454, 1110, 1063 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (5H, m, Ar*H*), 4.58 (1H, d, J=11.6, PhC*H*$_x$H$_y$), 4.52 (1H, d, J=11.6, PhCH$_x$*H*$_y$), 4.10–3.98 (1H, m, C*H*OH), 3.92 (1H, q, J=6.8, C*H*OBn), 2.88 (1H, br s, CHO*H*), 2.80 (1H, dd, J=18.0, 2.7, COC*H*$_x$H$_y$), 2.63 (1H, dd, J=18.0, 9.2, COCH$_x$*H*$_y$), 1.58–1.30 (4H, m, (C*H*$_2$)$_2$), 1.35 (3H, d, J=6.8, CH*Me*), 0.93 (3H, t, J=7.0, CH$_2$*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 214.1, 137.4, 128.5, 128.0, 127.8, 80.6, 71.9, 67.3, 44.2, 38.7, 18.7, 17.2, 13.9.

Minor aldol (**18h**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (1H, q, J=6.8, C*H*OBn), 2.72 (1H, dd, J=17.9, 3.4, COC*H*$_x$H$_y$). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 80.8, 44.1.

*4.3.11. (1S,4S)-4-Benzyloxy-1-hydroxy-1-phenyl-3-pentanone (**17e**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.15. IR (film) ν 3463 (br), 3085, 3058, 3026, 2976, 2862, 1710, 1601, 1492, 1451, 1023 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.26 (10H, m, Ar*H*), 5.18 (1H, dd, J=8.6, 3.8, C*H*OH), 4.57 (1H, d, J=11.7, PhCH$_x$H$_y$), 4.49 (1H, d, J=11.7, PhCH$_x$H$_y$), 3.93 (1H, q, J=6.8, C*H*OBn), 3.03 (1H, dd, J=17.9, 8.3, COC*H*$_x$H$_y$), 2.99 (1H, dd, J=17.9, 4.3, COCH$_x$*H*$_y$), 1.33 (3H, d, J=6.8, CH*Me*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38–7.20 (10H, m, Ar*H*), 5.38 (1H, d, J=4.4, CHO*H*), 5.09–5.02 (1H, m, C*H*OH), 4.51 (1H, d, J=11.6, PhC*H*$_x$H$_y$), 4.37 (1H, d, J=11.6, PhCH$_x$*H*$_y$), 3.97 (1H, q, J=6.8, C*H*OBn), 2.95 (1H, dd, J=16.0, 8.4, COC*H*$_x$H$_y$), 2.77 (1H, dd, J=16.0, 4.4, COCH$_x$*H*$_y$), 1.17 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.1, 142.9, 137.3, 128.5, 128.0, 127.8, 127.7, 125.7, 80.5, 71.9, 69.9, 46.2, 17.0. ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 209.9, 145.3, 138.1, 128.3, 128.1, 127.7, 127.6, 127.0, 125.8, 80.0, 70.8, 68.6, 47.4, 16.6. HRMS (+ESI): MNa$^+$, found 307.1311, $C_{18}H_{20}NaO_3$ requires 307.1304.

Minor aldol (**18e**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (1H, dd, J=8.6, 3.8, CHO*H*), 3.95 (1H, q, J=6.8, C*H*OBn), 2.92 (1H, dd, J=17.7, 3.1, COCH$_x$*H*$_y$), 1.33 (3H, d, J=6.8, CH*Me*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.37 (1H, d, J=4.4, CHO*H*), 5.04–4.99 (1H, m, C*H*OH), 4.45 (1H, d, J=11.6, PhC*H*$_x$H$_y$), 4.39 (1H, d, J=11.6, PhCH$_x$*H*$_y$), 4.01 (1H, q, J=6.8, C*H*OBn), 2.98 (1H, dd, J=16.0, 8.8, COC*H*$_x$H$_y$), 2.67 (1H, dd, J=16.0, 4.4, COCH$_x$*H*$_y$), 1.20 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 80.7, 46.1. ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 80.2, 68.8, 47.4, 16.6.

*4.3.12. (1S,4S)-4-Benzyloxy-1-hydroxy-1-(p-nitrophenyl)-3-pentanone (**17i**).* White solid. Mp 54–56 °C. R_f (75:25 hexanes/EtOAc) 0.10. IR (KBr) ν 3433 (br), 1709, 1598, 1509, 1449, 1347, 1077, 1012 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28–8.10 (2H, m, Ar*H*), 7.60–7.44 (2H, m, Ar*H*), 7.42–7.28 (5H, m, Ar*H*), 5.25 (1H, dd, J=9.1, 3.1, C*H*OH), 4.56 (1H, d, J=12.0, PhC*H*$_x$H$_y$), 4.52 (1H, d, J=12.0, PhCH$_x$*H*$_y$), 3.95 (1H, q, J=6.8, C*H*OBn), 3.04 (1H, dd, J=18.1, 3.1, COC*H*$_x$H$_y$), 2.93 (1H, dd, J=18.1, 9.1, COCH$_x$*H*$_y$), 1.35 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 212.6, 150.1, 147.3, 137.1, 128.6, 128.1, 127.8, 126.4, 123.7, 80.4, 71.9, 68.9, 46.0, 16.9.

Minor aldol (**18i**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (1H, dd, J=8.8, 3.3, C*H*OH), 4.58 (1H, d, J=11.6, PhC*H*$_x$H$_y$), 4.50 (1H, d, J=11.6, PhCH$_x$*H*$_y$), 3.96 (1H, q, J=6.8, C*H*OBn), 2.99 (1H, dd, J=18.0, 8.8, COC*H*$_x$H$_y$), 2.91 (1H, dd, J=18.0, 3.3, COCH$_x$*H*$_y$), 1.33 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 80.7.

*4.3.13. (1S,4S)-4-Benzyloxy-1-hydroxy-1-(p-methoxyphenyl)-3-pentanone (**17j**).* Yellowish oil. R_f (80:20 hexanes/EtOAc) 0.10. IR (film) ν 3467 (br), 1714, 1608, 1511, 1452, 1300, 1245, 1173, 1030 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.24 (7H, m, Ar*H*), 6.91–6.85 (2H, m, Ar*H*), 5.13 (1H, dd, J=8.4, 4.4, C*H*OH), 4.56 (1H, d, J=11.6, PhC*H*$_x$H$_y$), 4.48 (1H, d, J=11.6, PhCH$_x$*H*$_y$), 3.92 (1H, q, J=6.8, C*H*OBn), 3.80 (3H, s, *Me*O), 3.09 (1H, br s, CHO*H*), 3.07–2.84 (2H, m, COC*H*$_2$), 1.32 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.0, 159.1, 137.4, 135.1, 128.5, 127.9, 127.8, 126.9, 113.9, 80.5, 71.8, 69.5, 55.2, 46.2, 17.0.

Minor aldol (**18j**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (1H, dd, J=9.2, 3.2, C*H*OH), 1.33 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 80.7, 71.9, 69.5, 46.1, 17.0.

*4.3.14. (1S,4S)-4-Benzyloxy-1-(p-bromophenyl)-1-hydroxy-3-pentanone (**17k**).* Colourless oil. R_f (70:30 hexanes/EtOAc) 0.30. IR (film) ν 3446 (br), 1716, 1487, 1456, 1071, 1009 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.07 (9H, m, Ar*H*), 5.15–5.07 (1H, m, C*H*OH), 4.54 (1H, d, J=11.7, PhC*H*$_x$H$_y$), 4.49 (1H, d, J=11.7, PhCH$_x$*H*$_y$), 3.92 (1H, q, J=6.8, C*H*OBn), 3.28 (1H, br s, CHO*H*), 3.03–2.73 (2H, m, COC*H*$_2$), 1.32 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 212.9, 141.9, 137.2, 131.6, 128.5, 128.0, 127.8, 127.4, 121.4, 80.5, 71.9, 69.2, 46.1, 17.0.

Minor aldol (**18j**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (1H, dd, J=8.9, 3.4, C*H*OH), 4.53 (1H, d, J=11.9, PhC*H*$_x$H$_y$), 4.48 (1H, d, J=11.9,

PhCH$_x$H$_y$), 3.93 (1H, q, *J*=6.8, C*H*OBn). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.9, 80.7, 72.0, 46.0.

*4.3.15. (2S,5S)-2-Benzyloxy-5-hydroxy-6-methyl-6-hepten-3-one (**17f**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.15. IR (film) ν 3475 (br), 2977, 2930, 2862, 1713, 1447, 1083 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.24 (5H, m, Ar*H*), 5.04–5.00 (1H, m, C=C*H*$_x$H$_y$), 4.89–4.84 (1H, m, C=CH$_x$*H*$_y$), 4.59 (1H, d, *J*=11.7, PhC*H*$_x$H$_y$), 4.54–4.45 (1H, m, C*H*OH), 4.52 (1H, d, *J*=11.7, PhCH$_x$*H*$_y$), 3.95 (1H, q, *J*=6.9, C*H*OBn), 2.89–2.69 (3H, m, COC*H*$_2$ & CHO*H*), 1.74 (3H, br s, *Me*C=C), 1.36 (3H, d, *J*=6.9, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.2, 145.8, 137.4, 128.5, 128.0, 127.9, 111.2, 80.6, 71.9, 71.0, 42.8, 18.3, 17.1.

Minor aldol (**18f**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (1H, q, *J*=6.9, C*H*OBn). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 145.9, 111.2, 80.8, 71.9, 71.0, 42.8, 18.0.

*4.3.16. (2S,5S,6E)-2-Benzyloxy-5-hydroxy-6-octen-3-one (**17l**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.10. IR (film) ν 3451 (br), 2917, 2861, 1713, 1454, 1115 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m, Ar*H*), 5.72 (1H, dqd, *J*=15.4, 6.4, 1.1, CH=C*H*Me), 5.50 (1H, ddq, *J*=15.4, 6.6, 1.6, C*H*=CHMe), 4.58 (1H, d, *J*=11.7, PhC*H*$_x$H$_y$), 4.57–4.46 (1H, m, C*H*OH), 4.50 (1H, d, *J*=11.7, PhCH$_x$*H*$_y$), 3.92 (1H, q, *J*=6.8, C*H*OBn), 2.88–2.67 (3H, m, COC*H*$_2$ & CHO*H*), 1.69–1.67 (3H, m, CH=CH*Me*), 1.34 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.2, 137.4, 132.1, 128.5, 128.0, 127.8, 127.1, 80.6, 71.9, 68.5, 44.3, 17.6, 17.1.

Minor aldol (**18l**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (1H, dqd, *J*=15.4, 6.4, 1.1, CH=C*H*Me), 5.49 (1H, ddq, *J*=15.4, 6.6, 1.6, C*H*=CHMe), 4.56 (1H, d, *J*=11.8, PhC*H*$_x$H$_y$), 4.51 (1H, d, *J*=11.8, PhCH$_x$*H*$_y$), 3.93 (1H, q, *J*=6.8, C*H*OBn), 1.71–1.69 (3H, m, CH=CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.2, 132.1, 127.1, 80.7, 71.9, 68.4, 44.2, 17.0.

4.4. Synthesis of ketone 21 from 15a

*4.4.1. (2S,5S)-5-(tert-Butyldimethylsilyloxy)-2-(p-methoxybenzyloxy)-6-methyl-3-heptanone (**19**).* A mixture of **15a** (134 mg, 0.48 mmol, dr 86:14), 2,6-lutidine (83 μL, 0.72 mmol) and TBSOTf (140 μL, 0.60 mmol) in CH_2Cl_2 (1.8 mL) was stirred at rt overnight. It was diluted with CH_2Cl_2, washed with satd NH_4Cl, satd $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The resulting oil was purified by column chromatography (95:5 hexanes/EtOAc) to afford 134 mg (71% yield) of **19** (dr 86:14) as a colourless oil. R_f (95:5 hexanes/EtOAc) 0.45. IR (film) ν 2958, 2933, 2858, 1719, 1613, 1515, 1250, 1040 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (2H, m, Ar*H*), 6.90–6.87 (2H, m, Ar*H*), 4.52 (1H, d, *J*=11.4, ArC*H*$_x$H$_y$), 4.39 (1H, d, *J*=11.4, ArCH$_x$*H*$_y$), 4.17–4.13 (1H, m, C*H*OTBS), 3.88 (1H, q, *J*=6.8, C*H*OPMB), 3.80 (3H, s, *Me*O), 2.80 (1H, dd, *J*=17.2, 7.6, COC*H*$_x$H$_y$), 2.43 (1H, dd, *J*=17.2, 4.4, COCH$_x$*H*$_y$), 1.73 (1H, septd, *J*=6.8, 3.6, C*H*Me$_2$), 1.30 (3H, d, *J*=6.8, *Me*CHOPMB), 0.89 (3H, d, *J*=6.8, CH*Me*), 0.84 (9H, s, C*Me*$_3$), 0.83 (3H, *J*=6.8, CH*Me*), 0.06 (3H, s, Si*Me*), −0.01 (3H, s, Si*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.8, 159.4, 129.7, 129.6, 113.9, 80.5, 71.9, 71.5, 55.3, 40.7, 33.6, 25.9, 18.0, 17.5, 17.3, 17.1, −4.5, −4.8.

*4.4.2. (S)-5-(tert-Butyldimethylsilyloxy)-6-methyl-3-heptanone (**20**).* A 0.2 M solution of SmI_2 in THF (6.1 mL, 1.2 mmol) was slowly added via cannula to a solution of **19** (121 mg, 0.31 mmol) in 2:1 THF/MeOH (6.1 mL) at 0 °C under N_2. The dark green mixture was stirred for 1.5 h at 0 °C, quenched by addition of satd $NaHCO_3$ (10 mL) and vigorously stirred at rt for 10 min. Then it was partitioned with CH_2Cl_2 (50 mL) and satd $NaHCO_3$ (50 mL), and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was purified by column chromatography (95:5 hexanes/EtOAc) to afford 70 mg (89% yield) of **20** (er 86:14) as a colourless oil. R_f (95:5 hexanes/EtOAc) 0.30. $[\alpha]_D^{20}$ −41.9 (*c* 1.0, $CHCl_3$, 72% *ee*) [lit.[37] *ent*-**20** $[\alpha]_D^{20}$ +53.5 (*c* 0.85, $CHCl_3$)]. IR (film) ν 2960, 2933, 2860, 1719, 1474, 1252, 1088, 1053 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (1H, dt, *J*=8.0, 3.9, C*H*OTBS), 2.55 (1H, dd, *J*=14.8, 8.0, C*H*$_x$H$_y$CHOTBS), 2.45 (2H, q, *J*=7.2, C*H*$_2$CH$_3$), 2.32 (1H, dd, *J*=14.8, 3.9, CH$_x$*H*$_y$CHOTBS), 1.71 (1H, septd, *J*=6.8, 3.9, C*H*Me$_2$), 1.03 (t, *J*=7.2, CH$_2$*Me*), 0.88 (3H, d, *J*=6.8, CH*Me*), 0.85 (9H, s, C*Me*$_3$), 0.83 (3H, d, *J*=6.8, CH*Me*), 0.04 (3H, s, Si*Me*), −0.03 (3H, s, Si*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.9, 73.2, 45.6, 37.8, 33.8, 25.8, 18.0, 17.7, 17.2, 7.5, −4.7 (X2). HRMS (+FAB): MH^+, found 259.2091, $C_{14}H_{31}O_2Si$ requires 259.2093.

*4.4.3. (S)-5-Hydroxy-6-methyl-3-heptanone (**21**).* A 48% aqueous solution of HF (19 μL, 0.52 mmol) was added dropwise to a solution of **20** (41 mg, 0.16 mmol) in CH_3CN (1.8 mL) at rt. The reaction mixture was stirred for 3.5 h and diluted with CH_2Cl_2 (25 mL). The organic layer was washed with satd $NaHCO_3$, dried ($MgSO_4$) and concentrated. The resulting oil was purified by column chromatography (85:15 hexanes/EtOAc) to afford 16 mg (70% yield) of **21** (er 86:14) as a colourless oil. R_f (85:15 hexanes/EtOAc) 0.20. $[\alpha]_D^{20}$ −46.7 (*c* 1.6, $CHCl_3$, 72% *ee*) [lit.[37] *ent*-**21** $[\alpha]_D^{20}$ +53.5 (*c* 0.83, $CHCl_3$)]. IR (film) ν 3477 (br), 2964, 1710, 1465, 1412, 1380, 1115 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (1H, ddd, *J*=9.6, 5.8, 2.4, C*H*OH), 2.59 (1H, dd, *J*=17.2, 2.4, C*H*$_x$H$_y$CHOH), 2.50 (1H, dd, *J*=17.2, 9.6, CH$_x$*H*$_y$CHOH), 2.48 (2H, q, *J*=7.2, C*H*$_2$CH$_3$), 1.74–1.63 (1H, m, C*H*Me$_2$), 1.07 (3H, t, *J*=7.2, CH$_2$*Me*), 0.94 (3H, d, *J*=6.8, CH*Me*), 0.92 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.1, 72.3, 45.6, 36.8, 33.0, 18.3, 17.8, 7.6.

4.5. Synthesis of carboxylic acid 22 from 17a

A mixture of **17a** (293 mg, 1.17 mmol, dr 85:15) and 10% Pd/C (300 mg) in EtOH (50 mL) was hydrogenated with H_2 (1 atm) at rt for 3 h. The reaction mixture was filtered on Celite®, eluted with CH_2Cl_2 and concentrated to obtain 178 mg (1.11 mmol) of a colourless oil, which was used in the next step without further purification. A mixture of this oil and $NaIO_4$ (1.95 g, 9.0 mmol) in 2:1 MeOH/H_2O (10 mL) was stirred for 1 h at rt. Then, it was diluted with Et_2O (10 mL), cooled to 0 °C and 0.5 M HCl was slowly added to reach pH 1. The mixture was partitioned with Et_2O (10 mL) and H_2O (10 mL), and the aqueous layer was extracted with Et_2O (4×10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (95:5 CH_2Cl_2/MeOH) to afford 70 mg (49% overall yield) of **22** (er 85:15) as a colourless oil. R_f (95:5 CH_2Cl_2/MeOH) 0.20. $[\alpha]_D^{20}$ −25.3 (*c* 1.2, $CHCl_3$, 70% *ee*) [lit.[20b] $[\alpha]_D^{25}$ −40.7 (*c* 3.0, $CHCl_3$)]. IR (film) ν 3293 (br), 2960, 2931, 2876, 2637, 1715, 1407, 1286, 1182 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (1H, ddd, *J*=9.1, 5.9, 3.2, C*H*OH), 2.58 (1H, dd, *J*=16.4, 3.2, COC*H*$_x$H$_y$), 2.48 (1H, dd, *J*=16.4, 9.1, COCH$_x$*H*$_y$), 1.82–1.68 (1H, m, C*H*Me$_2$), 0.97 (3H, d, *J*=6.9, *Me*), 0.95 (3H, d, *J*=6.9, *Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 178.1, 72.8, 38.4, 33.2, 18.3, 17.7.

4.6. Spectroscopic data of aldols from ketones 3–5

*4.6.1. (3S,6S)-6-Benzyloxy-3-hydroxy-2,8-dimethyl-5-nonanone (**23a**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.30. IR (film) ν 3501 (br), 2956, 2927, 2869, 1714, 1467, 1451, 1095, 1045, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m, Ar*H*), 4.60 (1H, d, *J*=11.4, PhC*H*$_x$H$_y$), 4.40 (1H, d, *J*=11.4, PhCH$_x$*H*$_y$), 3.84 (1H, dd, *J*=9.5, 4.2, C*H*OBn), 3.83–3.78 (1H, m, C*H*OH), 2.87 (1H, d, *J*=3.2, CHO*H*), 2.71 (1H, dd, *J*=17.7, 2.4, COC*H*$_x$H$_y$), 2.60 (1H, dd, *J*=17.7, 9.4, COCH$_x$*H*$_y$), 1.89–1.76 (1H, m, CH$_2$C*H*Me$_2$), 1.76–1.64 (1H, m, CH(OH) C*H*Me$_2$), 1.62 (1H, ddd, *J*=13.9, 9.5, 5.2, C*H*$_x$H$_y$CHMe), 1.36 (1H, ddd, *J*=13.9, 8.8, 4.2, CH$_x$*H*$_y$CHMe), 0.94 (3H, d, *J*=6.4, CH(OH)CH*Me*), 0.93 (3H, d, *J*=6.8, CH$_2$CH*Me*), 0.92 (3H, d, *J*=6.8, CH(OH)CH*Me*), 0.85 (3H, d, *J*=6.4, CH$_2$CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.3,

137.3, 128.5, 128.1 (×2), 83.6, 72.7, 72.1, 41.1, 41.0, 33.1, 24.5, 23.2, 21.6, 18.4, 17.7. HRMS (+ESI): MH^+, found 293.2115, $C_{18}H_{29}O_3$ requires 293.2111.

Minor aldol (**24a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (1H, d, J=11.6, PhCH_xH_y), 2.69 (1H, dd, J=17.6, 2.4, COCH_xH_y), 2.57 (1H, dd, J=17.6, 9.6, COCH$_x$$H_y$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 84.0, 72.8, 72.2, 40.9.

*4.6.2. (1S,4S)-4-Benzyloxy-1-hydroxy-6-methyl-1-phenyl-3-heptanone (**23e**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.20. IR (film) ν 3465 (br), 3027, 2957, 2929, 2867, 1714, 1556, 1494, 1456, 1383, 1087, 1051, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (10H, m, Ar*H*), 5.17 (1H, ddd, J=8.8, 3.6, 3.4, C*H*OH), 4.57 (1H, d, J=11.6, PhCH_xH_y), 4.35 (1H, d, J=11.6, PhCH$_x$$H_y$), 3.83 (1H, dd, J=9.6, 4.4, C*H*OBn), 3.21 (1H, d, J=3.4, CHO*H*), 3.00 (1H, dd, J=17.8, 8.8, COCH_xH_y), 2.91 (1H, dd, J=17.8, 3.6, COCH$_x$$H_y$), 1.85–1.72 (1H, m, C*H*Me$_2$), 1.64–1.54 (1H, m, CH_xH_yCHMe$_2$), 1.32 (1H, ddd, J=14.0, 8.6, 4.4, CH$_x$$H_y$CHMe$_2$), 0.90 (3H, d, J=6.8, CH*Me*), 0.82 (3H, d, J=6.4, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.9, 142.9, 137.3, 128.5 (×2), 128.0 (×2), 127.7, 125.7, 83.5, 72.6, 69.9, 46.0, 40.8, 24.4, 23.2, 21.6.

Minor aldol (**24e**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (1H, ddd, J=8.8, 3.6, 3.4, C*H*OH), 4.51 (1H, d, J=11.6, PhCH_xH_y), 4.37 (1H, d, J=11.6, PhCH$_x$$H_y$), 3.84 (1H, dd, J=9.6, 4.0, C*H*OBn), 3.18 (1H, d, J=3.4, CHO*H*), 2.97 (1H, dd, J=17.6, 8.8, COCH_xH_y), 2.87 (1H, dd, J=17.6, 3.6, COCH$_x$$H_y$), 0.90 (3H, d, J=6.4, CH*Me*), 0.82 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 213.8, 127.7, 125.6, 83.8, 72.7, 40.7, 24.4, 23.1, 21.7.

*4.6.3. (3S,6S)-6-Benzyloxy-3-hydroxy-2,8-dimethyl-1-nonen-5-one (**23f**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.25. IR (film) ν 3485 (br), 2955, 2928, 2867, 1715, 1454, 1385, 1367, 1087, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.26 (5H, m, Ar*H*), 5.03 (1H, br s, C=CH_xH_y), 4.87 (1H, br s, C=CH$_x$$H_y$), 4.61 (1H, d, J=11.4, PhCH_xH_y), 4.55–4.49 (1H, m, C*H*OH), 4.40 (1H, d, J=11.4, PhCH$_x$$H_y$), 3.85 (1H, dd, J=9.5, 4.4, C*H*OBn), 2.89 (1H, d, J=3.2, CHO*H*), 2.85–2.70 (2H, m, COCH_2), 1.89–1.75 (1H, m, C*H*Me$_2$), 1.75 (3H, br s, *Me*C=CH$_2$), 1.62 (1H, ddd, J=13.9, 9.5, 5.2, CH_xH_yCHMe$_2$), 1.37 (1H, ddd, J=13.9, 8.7, 4.4, CH$_x$$H_y$CHMe$_2$), 0.93 (3H, d, J=6.4, CH*Me*), 0.85 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 214.1, 145.8, 137.3, 128.5, 128.1, 128.0, 111.2, 83.5, 72.6, 71.0, 42.6, 41.0, 24.5, 23.2, 21.6, 18.3.

Minor aldol (**24f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (1H, d, J=11.6, PhCH_xH_y), 3.90 (1H, dd, J=9.4, 4.2, C*H*OBn), 2.87 (1H, d, J=3.2, CHO*H*), 1.74 (3H, br s, *Me*C=CH$_2$). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 111.2, 83.9, 72.8, 40.8.

*4.6.4. (2S,5S)-2-Benzyloxy-5-hydroxy-6-methyl-1-phenyl-3-heptanone (**25a**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.20. IR (film) ν 3498 (br), 3024, 2956, 2926, 2871, 1710, 1492, 1453, 1381, 1086 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.13 (10H, m, Ar*H*), 4.53 (1H, d, J=11.6, PhCH_xH_yO), 4.40 (1H, d, J=11.6, PhCH$_x$$H_y$O), 4.03 (1H, dd, J=8.6, 4.4, C*H*OBn), 3.78–3.66 (1H, m, C*H*OH), 3.04 (1H, dd, J=14.0, 4.4, PhCH_xH_y), 2.93 (1H, dd, J=14.0, 8.6, PhCH$_x$$H_y$), 2.80 (1H, d, J=3.6, CHO*H*), 2.65–2.47 (2H, d, COCH_2), 1.69–1.56 (1H, m, C*H*Me$_2$), 0.87 (3H, d, J=6.4, CH*Me*), 0.84 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 214.3, 137.1, 136.8, 129.5, 128.4 (×2), 127.9, 127.8, 126.7, 85.6, 72.8, 71.9, 42.3, 38.4, 33.0, 18.3, 17.7. HRMS (+ESI): MNH_4^+, found 344.2221, $C_{21}H_{30}NO_3$ requires 344.2220.

Minor aldol (**26a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (1H, d, J=11.6, PhCH_xH_yO), 4.39 (1H, d, J=11.6, PhCH$_x$$H_y$O), 2.77 (1H, d, J=3.6, CHOH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 129.5, 127.9, 85.9, 72.9, 72.1, 42.2, 38.5, 33.1, 18.3.

*4.6.5. (1S,4S)-4-Benzyloxy-1-hydroxy-1,5-diphenyl-3-pentanone (**25e**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.15. IR (film) ν 3464 (br), 3057, 3028, 2862, 1713, 1696, 1650, 1557, 1493, 1455, 1086, 1026 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.10 (15H, m, Ar*H*), 5.07–5.00 (1H, m, C*H*OH), 4.50 (1H, d, J=11.6, PhCH_xH_yO), 4.36 (1H, d, J=11.6, PhCH$_x$$H_y$O), 4.03 (1H, dd, J=7.7, 4.4, C*H*OBn), 3.21 (1H, d, J=3.2, CHO*H*), 3.01 (1H, dd, J=14.1, 4.4, PhCH_xH_y), 2.91 (1H, dd, J=14.1, 7.7, PhCH$_x$$H_y$), 2.91 (1H, dd, J=18.0, 9.4, COCH_xH_y), 2.76 (1H, dd, J=18.0, 3.1, COCH$_x$$H_y$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.1, 142.8, 137.1, 136.6, 129.6, 128.5, 128.4, 127.9, 127.8, 127.6, 126.8, 125.6, 85.5, 72.7, 69.7, 47.3, 38.3. HRMS (+ESI): MNH_4^+, found 378.2068, $C_{24}H_{28}NO_3$ requires 378.2064.

*4.6.6. (2S,5S)-2-Benzyloxy-5-hydroxy-6-methyl-1-phenyl-6-hepten-3-one (**25f**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.20. IR (film) ν 3475 (br), 3062, 3023, 2916, 2860, 1709, 1648, 1493, 1450, 1081, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.13 (10H, m, Ar*H*), 4.98–4.95 (1H, m, C=CH_xH_y), 4.85–4.81 (1H, m, C=CH$_x$$H_y$), 4.54 (1H, d, J=11.6, PhCH_xH_yO), 4.40 (1H, d, J=11.6, PhCH$_x$$H_y$O), 4.46–4.37 (1H, m, C*H*OH), 4.04 (1H, dd, J=8.0, 4.4, C*H*OBn), 3.05 (1H, dd, J=14.0, 4.4, PhCH_xH_y), 2.93 (1H, dd, J=14.0, 8.0, PhCH$_x$$H_y$), 2.85 (1H, d, J=3.2, CHO*H*), 2.71 (1H, dd, J=17.8, 9.2, COCH_xH_y), 2.61 (1H, dd, J=17.8, 3.2, COCH$_x$$H_y$), 1.66 (3H, br s, *Me*C=CH$_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.2, 145.7, 137.1, 136.7, 129.6, 128.4 (×2), 127.9, 127.8, 126.8, 111.1, 85.5, 72.7, 70.7, 43.9, 38.3, 18.3.

Minor aldol (**26f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99–4.97 (1H, m, C=CH_xH_y), 4.86–4.84 (1H, m, C=CH$_x$$H_y$), 4.49 (1H, d, J=11.6, PhCH_xH_yO), 4.39 (1H, d, J=11.6, PhCH$_x$$H_y$O), 2.79 (1H, d, J=3.2, CHO*H*), 1.69 (3H, br s, *Me*C=CH$_2$).

*4.6.7. (3S,6S)-3-Benzyloxy-6-hydroxy-2,7-dimethyl-4-octanone (**27a**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.25. IR (film) ν 3501 (br), 2956, 2930, 2873, 1712, 1468, 1455, 1387, 1091, 1070, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (5H, m, Ar*H*), 4.58 (1H, d, J=11.6, PhCH_xH_y), 4.40 (1H, d, J=11.6, PhCH$_x$$H_y$), 3.86–3.73 (1H, m, C*H*OH), 3.48 (1H, d, J=6.8, C*H*OBn), 2.96 (1H, d, J=3.4, CHO*H*), 2.66 (1H, dd, J=17.9, 3.0, COCH_xH_y), 2.59 (1H, dd, J=17.9, 8.9, COCH$_x$$H_y$), 2.08–1.95 (1H, m, BnOCHC*H*Me$_2$), 1.76–1.63 (1H, m, CHOHC*H*Me$_2$), 0.98 (3H, d, J=6.7, BnOCHCH*Me*), 0.95 (9H, m, BnOCHCH*Me* & CHOHCH*Me*$_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.2, 137.4, 128.4, 128.0 (×2), 90.3, 73.1, 72.0, 41.8, 33.1, 31.0, 18.8, 18.3, 18.1, 17.7.

Minor aldol (**28a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (1H, d, J=11.6, PhCH_xH_y), 3.46 (1H, d, J=6.8, C*H*OBn), 2.91 (1H, d, J=3.4, CHO*H*), 2.73 (1H, dd, J=17.9, 2.0, COCH_xH_y), 2.48 (1H, dd, J=17.9, 9.9, COCH$_x$$H_y$), 0.99 (3H, d, J=6.6, BnOCHCH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 215.1, 128.5, 128.0 (×2), 90.8, 73.2, 72.1, 41.7, 33.1, 30.9, 18.6, 18.2, 17.7.

*4.6.8. (1S,4S)-4-Benzyloxy-1-hydroxy-5-methyl-1-phenyl-3-hexanone (**27e**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.20. IR (film) ν 3467 (br), 2961, 2930, 2899, 2870, 1715, 1496, 1452, 1384, 1069, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.22 (10H, m, Ar*H*), 5.17 (1H, d, J=8.8, C*H*OH), 4.58 (1H, d, J=11.6, PhCH_xH_y), 4.34 (1H, d, J=11.6, PhCH$_x$$H_y$), 3.47 (1H, d, J=6.8, C*H*OBn), 3.30 (1H, br s, CHO*H*), 3.02 (1H, dd, J=18.0, 9.2, COCH_xH_y), 2.86 (1H, dd, J=18.0, 3.0, COCH$_x$$H_y$), 2.06–1.92 (1H, m, C*H*Me$_2$), 0.96 (3H, d, J=6.8, CH*Me*), 0.88 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.9, 142.9, 137.4, 128.5, 128.4, 127.9 (×2), 127.7, 125.7, 90.1, 73.0, 69.8, 46.8, 31.0, 18.7, 18.1. HRMS (+ESI): MNH_4^+, found 330.2066, $C_{20}H_{28}NO_3$ requires 330.2064.

Minor aldol (**28e**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (1H, d, J=11.6, PhCH_xH_y), 3.23 (1H, br s, CHO*H*), 0.88 (3H, d, J=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 127.6, 125.7, 90.5, 73.1, 69.8, 30.8, 18.6, 18.2.

*4.6.9. (3S,6S)-3-Benzyloxy-6-hydroxy-2,7-dimethyl-7-octen-4-one (**27f**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.25. IR (film) ν 3482 (br), 2961, 2929, 2911, 2872, 1710, 1454, 1386, 1071, 1027 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (5H, m, Ar*H*), 5.02 (1H, br s, C=CH_xH_y), 4.86 (1H, br s, C=CH$_x$$H_y$), 4.63 (1H, d, J=11.6, PhCH_xH_y), 4.56–4.44

(1H, m, C*H*OH), 4.40 (1H, d, *J*=11.6, PhCH$_x$*H*$_y$), 3.49 (1H, d, *J*=6.8, C*H*OBn), 2.97 (1H, d, *J*=3.2, CHO*H*), 2.80 (1H, dd, *J*=18.0, 9.4, COC*H*$_x$H$_y$), 2.68 (1H, dd, *J*=18.0, 2.8, COC*H*$_x$H$_y$), 2.10–1.95 (1H, m, C*H*Me$_2$), 1.74 (3H, br s, *Me*C=CH$_2$), 0.98 (3H, d, *J*=6.4, CH*Me*), 0.91 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 214.1, 145.8, 137.4, 128.4, 128.0 (×2), 111.2, 90.2, 73.0, 70.9, 43.4, 31.0, 18.7, 18.3, 18.1.

Minor aldol (**28f**). ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.56 (1H, d, *J*=11.6, PhC*H*$_x$H$_y$), 3.48 (1H, d, *J*=6.8, C*H*OBn), 2.91 (1H, d, *J*=3.2, CHO*H*), 1.73 (3H, br s, *Me*C=CH$_2$), 0.99 (3H, d, *J*=6.4, CH*Me*). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 213.9, 128.5, 111.1, 90.6, 73.2, 43.4, 30.8, 18.6, 18.3, 18.2.

4.7. Spectroscopic data for aldols from aldehyde 29

*4.7.1. (2S,5S,6S)-7-(tert-Butyldiphenylsilyloxy)-5-hydroxy-2-(p-methoxybenzyloxy)-6-methyl-3-heptanone (**31**).* Colourless oil. R_f (75:25 hexanes/EtOAc) 0.30. $[\alpha]_D^{20}$ −29.8 (*c* 1.3, CHCl$_3$, 86% *de*). IR (film) ν 3507 (br), 3071, 2933, 1716, 1612, 1514, 1391, 1366, 1249, 1111, 1036 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68–7.64 (4H, m, Ar*H*), 7.45–7.36 (6H, m, Ar*H*), 7.28–7.24 (2H, m, Ar*H*), 6.88–6.85 (2H, m, Ar*H*), 4.51 (1H, d, *J*=11.2, PhC*H*$_x$H$_y$), 4.43 (1H, d, *J*=11.2, PhCH$_x$*H*$_y$), 4.40–4.30 (1H, m, C*H*OH), 3.91 (1H, q, *J*=6.8, C*H*OPMB), 3.79 (3H, s, *Me*O), 3.71 (1H, dd, *J*=10.0, 4.7, C*H*$_x$H$_y$OSi), 3.66 (1H, dd, *J*=10.0, 6.1, CH$_x$*H*$_y$OSi), 3.05 (1H, br s, CHO*H*), 2.81 (1H, dd, *J*=17.5, 9.2, COC*H*$_x$H$_y$), 2.67 (1H, dd, *J*=17.5, 3.3, COCH$_x$*H*$_y$), 1.80–1.71 (1H, m, C*H*CH$_2$OSi), 1.31 (3H, d, *J*=6.8, CH*Me*), 1.06 (9H, s, C*Me*$_3$), 0.93 (3H, d, *J*=7.0, CH*Me*). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 213.3, 159.4, 135.6, 135.5, 133.3, 133.2, 129.7 (×2), 129.6, 129.5, 127.7, 113.9, 80.3, 71.5, 68.9, 67.2, 55.3, 41.9, 39.8, 26.9, 19.2, 17.2, 10.9. HRMS (+FAB): MH$^+$, found 535.2869, $C_{32}H_{43}O_5Si$ requires 535.2880.

Minor aldol (**32**). ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.78 (3H, s, *Me*O), 1.88–1.78 (1H, m, C*H*CH$_2$OSi), 0.87 (3H, d, *J*=7.0, CH*Me*). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 80.4, 71.0, 67.5, 67.1, 42.2, 40.2, 17.1, 13.3.

*4.7.2. (2S,5S,6S)-2-Benzyloxy-7-(tert-butyldiphenylsilyloxy)-5-hydroxy-6-methyl-3-heptanone (**33**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.25. $[\alpha]_D^{20}$ −24.5 (*c* 1.1, CHCl$_3$, 82% *de*). IR (film) ν 3512 (br), 2928, 1715, 1469, 1452, 1427, 1109 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70–7.64 (4H, m, Ar*H*), 7.46–7.26 (11H, m, Ar*H*), 4.59 (1H, d, *J*=11.6, PhC*H*$_x$H$_y$), 4.50 (1H, d, *J*=11.6, PhCH$_x$*H*$_y$), 4.39–4.31 (1H, m, C*H*OH), 3.93 (1H, q, *J*=6.8, C*H*OBn), 3.70 (1H, dd, *J*=10.2, 4.8, C*H*$_x$H$_y$OSi), 3.66 (1H, dd, *J*=10.2, 6.2, CH$_x$*H*$_y$OSi), 3.08 (1H, br s, CHO*H*), 2.82 (1H, dd, *J*=17.4, 9.3, COC*H*$_x$H$_y$), 2.68 (1H, dd, *J*=17.4, 3.2, COCH$_x$*H*$_y$), 1.81–1.71 (1H, m, C*H*CH$_2$OSi), 1.34 (3H, d, *J*=6.8, CH*Me*), 1.05 (9H, s, C*Me*$_3$), 0.92 (3H, d, *J*=7.0, CH*Me*). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 213.2, 137.5, 135.6 (×2), 133.3, 133.2, 129.8, 129.7, 128.5, 127.9, 127.8, 127.7 (×2), 80.6, 71.9, 69.0, 67.3, 42.0, 39.8, 26.9, 19.2, 17.2, 11.0. HRMS (+ESI): MH$^+$, found: 505.2772, $C_{31}H_{41}O_4Si$ requires 505.2768.

Minor aldol (**34**). ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.98 (1H, q, *J*=6.9, C*H*OBn), 2.65 (1H, dd, *J*=16.8, 2.8, COCH$_x$*H*$_y$). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 80.6, 71.0, 42.1, 40.1.

*4.7.3. (2R,5R,6S)-2-Benzyloxy-7-(tert-butyldiphenylsilyloxy)-5-hydroxy-6-methyl-3-heptanone (**35**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.25. IR (film) ν 3499 (br), 2929, 1715, 1472, 1454, 1424, 1106 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71–7.62 (4H, m, Ar*H*), 7.47–7.26 (11H, m, Ar*H*), 4.61 (1H, d, *J*=11.7, PhC*H*$_x$H$_y$), 4.50 (1H, d, *J*=11.7, PhCH$_x$*H*$_y$), 4.20–4.12 (1H, m, C*H*OH), 3.96 (1H, q, *J*=6.8, C*H*OBn), 3.73 (1H, dd, *J*=10.3, 4.8, C*H*$_x$H$_y$OSi), 3.66 (1H, dd, *J*=10.3, 6.6, CH$_x$*H*$_y$OSi), 3.55 (1H, d, *J*=3.2, CHO*H*), 2.79–2.75 (2H, m, COC*H*$_2$), 1.91–1.79 (1H, m, C*H*CH$_2$OSi), 1.34 (3H, d, *J*=6.8, CH*Me*), 1.05 (9H, s, C*Me*$_3$), 0.87 (3H, d, *J*=6.9, CH*Me*). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 213.3, 137.6, 135.6, 133.2, 129.7, 128.5, 127.8, 127.7, 80.7, 71.8, 70.8, 67.2, 42.1, 40.2, 26.8, 19.2, 17.2, 13.2.

Minor aldol (**36**). ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.56 (1H, d, *J*=11.8, PhC*H*$_x$H$_y$), 4.50 (1H, d, *J*=11.8, PhCH$_x$*H*$_y$), 4.35–4.28 (1H, m, C*H*OH), 3.96 (1H, q, *J*=6.9, C*H*OBn), 2.83 (1H, dd, *J*=17.1, 9.4, COC*H*$_x$H$_y$), 2.58 (1H, dd, *J*=17.1, 3.0, COCH$_x$*H*$_y$), 1.05 (9H, s, C*Me*$_3$), 0.91 (3H, d, *J*=7.0, CH*Me*). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 213.1, 80.8, 68.7, 67.2, 13.1.

4.8. Spectroscopic data for aldols from aldehydes 30 and *ent*-30

*4.8.1. (2S,5S,6R)-6-(tert-Butyldiphenylsilyloxy)-5-hydroxy-2-(p-methoxybenzyloxy)-3-heptanone (**37**).* Colourless oil. R_f (85:15 hexanes/EtOAc) 0.15. $[\alpha]_D^{20}$ −29.0 (*c* 1.2, CHCl$_3$, 90% *de*). IR (film) ν 3521 (br), 2934, 1716, 1612, 1427, 1110 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70–7.66 (4H, m, Ar*H*), 7.44–7.34 (6H, m, Ar*H*), 7.26–7.24 (2H, m, Ar*H*), 6.87–6.85 (2H, m, Ar*H*), 4.50 (1H, d, *J*=11.3, PhC*H*$_x$H$_y$), 4.41 (1H, d, *J*=11.3, PhCH$_x$*H*$_y$), 4.05–4.01 (1H, m, C*H*OH), 3.88 (1H, q, *J*=6.8, C*H*OPMB), 3.79 (3H, s, *Me*O), 3.89–3.81 (1H, m, C*H*OSi), 2.74–2.72 (2H, m, COC*H*$_2$), 1.28 (3H, d, *J*=6.8, *Me*CHOPMB), 1.07 (9H, s, C*Me*$_3$), 1.02 (3H, d, *J*=6.4, CH*Me*). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 213.0, 159.4, 135.9, 134.2, 133.5, 129.8, 129.7, 129.6, 129.5, 127.7, 127.5, 113.9, 80.2, 72.1, 71.6, 71.5, 55.3, 39.8, 27.0, 19.3, 18.3, 17.1. HRMS (+FAB): MH$^+$, found 521.2706, $C_{31}H_{41}O_5Si$ requires 521.2723.

*4.8.2. (2S,5S,6R)-2-Benzyloxy-6-(tert-butyldiphenylsilyloxy)-5-hydroxy-3-heptanone (**39**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.25. $[\alpha]_D^{20}$ −30.1 (*c* 1.4, CHCl$_3$, 82% *de*). IR (film) ν 3511 (br), 2930, 2852, 1713, 1425, 1106 cm^{-1}. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69–7.62 (4H, m, Ar*H*), 7.44–7.25 (11H, m, Ar*H*), 4.55 (1H, d, *J*=11.5, PhC*H*$_x$H$_y$), 4.47 (1H, d, *J*=11.5, PhCH$_x$*H*$_y$), 4.04–3.99 (1H, m, C*H*OH), 3.89 (1H, q, *J*=6.8, C*H*OBn), 3.82 (1H, qd, *J*=6.3, 4.0, C*H*OSi), 2.79–2.61 (2H, m, COC*H*$_2$), 1.29 (3H, d, *J*=6.8, *Me*CHOBn), 1.04 (9H, s, C*Me*$_3$), 1.00 (3H, d, *J*=6.3, CH*Me*). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 212.8, 137.5, 135.9 (×2), 134.1, 133.5, 129.8, 129.7, 128.5, 127.9, 127.8, 127.7, 127.5, 80.6, 72.1, 71.8, 71.6, 39.8, 27.0, 19.3, 18.4, 17.1. HRMS (+ESI): MNH$_4^+$, found 508.2867, $C_{30}H_{42}NO_4Si$ requires 508.2877.

*4.8.3. (2S,5S,6S)-6-(tert-Butyldiphenylsilyloxy)-5-hydroxy-2-(p-methoxybenzyloxy)-3-heptanone (**41**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.15. $[\alpha]_D^{20}$ −40.0 (*c* 1.0, CHCl$_3$). IR (film) ν 3500 (br), 2928, 2853, 1715, 1614, 1512, 1250, 1109, 1032 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70–7.62 (4H, m, Ar*H*), 7.47–7.32 (6H, m, Ar*H*), 7.29–7.22 (2H, m, Ar*H*), 6.91–6.83 (2H, m, Ar*H*), 4.49 (1H, d, *J*=11.2, PhC*H*$_x$H$_y$), 4.41 (1H, d, *J*=11.2, PhCH$_x$*H*$_y$), 4.05–3.95 (1H, m, C*H*OH), 3.90 (1H, q, *J*=6.8, C*H*OPMB), 3.87–3.81 (1H, m, C*H*OSi), 3.80 (3H, s, *Me*O), 2.76–2.70 (2H, d, COC*H*$_2$), 1.29 (3H, d, *J*=6.8, *Me*CHOPMB), 1.05 (9H, s, C*Me*$_3$), 1.04 (3H, d, *J*=6.8, CH*Me*). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 213.0, 159.4, 135.8 (×2), 134.0, 133.4, 129.8, 129.7, 129.6, 129.5, 127.7, 127.5, 113.9, 80.4, 71.7, 71.5, 71.2, 55.3, 39.9, 27.0, 19.3, 18.6, 17.2. HRMS (+ESI): MNa$^+$, found 543.2528, $C_{31}H_{40}O_5NaSi$ requires 543.2537.

*4.8.4. (2S,5S,6S)-2-Benzyloxy-6-(tert-butyldiphenylsilyloxy)-5-hydroxy-3-heptanone (**42**).* Colourless oil. R_f (80:20 hexanes/EtOAc) 0.20. $[\alpha]_D^{20}$ −41.9 (*c* 1.1, CHCl$_3$). IR (film) ν 3504 (br), 2923, 2851, 1710, 1420, 1108 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69–7.63 (4H, m, Ar*H*), 7.46–7.27 (11H, m, Ar*H*), 4.57 (1H, d, *J*=11.6, PhC*H*$_x$H$_y$), 4.48 (1H, d, *J*=11.6, PhCH$_x$*H*$_y$), 4.04–3.96 (1H, m, C*H*OH), 3.92 (1H, q, *J*=6.8, C*H*OBn), 3.83 (1H, qd, *J*=6.0, 4.8, C*H*OSi), 2.82–2.68 (3H, m, COC*H*$_2$ & CHO*H*), 1.32 (3H, d, *J*=6.8, *Me*CHOBn), 1.05 (9H, s, C*Me*$_3$), 1.04 (3H, d, *J*=6.0, *Me*CH). ^{13}C NMR (75.4 MHz, CDCl$_3$) δ 212.9, 137.5, 135.9, 135.8, 134.0, 133.4, 129.8, 129.7, 128.5, 127.9, 127.8, 127.7, 127.6, 80.7, 71.8, 71.7, 71.2, 40.0, 27.0, 19.3, 18.7, 17.2. HRMS (+ESI): 2MNa$^+$, found 1003.4963, $C_{60}H_{76}O_8NaSi_2$ requires 1003.4970.

4.9. Synthesis of lactones 45 and 48

*4.9.1. (3S,4R)-3-Hydroxy-4-methyl-γ-butyrolactone (**45**).* Experimental procedure described for the synthesis of **22** was applied to **39**

(243 mg, 0.50 mmol, dr 91:9) to afford 159 mg (0.43 mmol) of **44** as a brownish oil, which was used in the next step without further purification. A 48% aqueous solution of HF (0.15 mL, 4.3 mmol) was added dropwise to a solution of **44** in CH_3CN (4.0 mL) at rt. The reaction mixture was stirred for 24 h and diluted with CH_2Cl_2 (30 mL). Then 2 M HCl was slowly added to reach pH 1 and the mixture was concentrated. It was treated again with CH_2Cl_2, dried ($MgSO_4$) and further concentrated. The resulting brownish oil was purified by column chromatography (hexanes/EtOAc from 65:35 to 35:65) to afford 20 mg (40% overall yield) of **45** (dr 91:9) as a colourless oil. R_f (50:50 hexanes/EtOAc) 0.10. $[\alpha]_D^{20}$ +10.3 (*c* 0.9, $CHCl_3$, 82% *de*) [lit.[30] $[\alpha]_D$ +10.87 (*c* 2.42, $CHCl_3$); lit.[30] $[\alpha]_D$ +10.0 (*c* 1.59, $CHCl_3$); lit.[30] $[\alpha]_D^{25}$ +10.91 (*c* 1.27, $CHCl_3$)]. IR (film) ν 3429 (br), 1766, 1173, 1052 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.50 (1H, qd, *J*=6.6, 3.1, MeC*H*), 4.25 (1H, ddd, *J*=6.6, 3.9, 3.1, C*H*OH), 2.86 (1H, dd, *J*=17.9, 6.6, $COCH_xH_y$), 2.52 (1H, dd, *J*=17.9, 3.9, $COCH_xH_y$), 1.38 (3H, d, *J*=6.6, *Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.0, 83.9, 72.9, 37.4, 18.5.

*4.9.2. (3S,4S)-3-Hydroxy-4-methyl-γ-butyrolactone (**48**).* Experimental procedure described for the synthesis of **45** was applied to **42** (347 mg, 0.71 mmol) to afford 41 mg (50% overall yield) of **48** as a colourless oil. R_f (50:50 hexanes/EtOAc) 0.10. $[\alpha]_D^{20}$ −72.4 (*c* 0.5, $CHCl_3$) [lit.[31] $[\alpha]_D^{25}$ −60.0 (*c* 1.57, $CHCl_3$, 78% *ee*)]. IR (film) ν 3432 (br), 1766, 1167, 1054 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (1H, qd, *J*=6.5, 3.7, *Me*C*H*), 4.24 (1H, ddd, *J*=5.6, 3.7, 1.2, C*H*OH), 2.81 (1H, dd, *J*=17.7, 5.6, $COCH_xH_y$), 2.57 (1H, dd, *J*=17.7, 1.2, $COCH_xH_y$), 1.44 (3H, d, *J*=6.5, *Me*). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 176.6, 81.1, 69.4, 39.3, 13.6.

4.10. Synthesis of C12–C16 fragment of epothilone B

*4.10.1. (2S,3S,5R,6S)-2-(tert-Butyldiphenylsilyloxy)-6-(p-methoxybenzyloxy)-3,5-heptanediol (**49**).* 1.0 M solution of DIBALH in hexanes (450 μL, 0.45 mmol) was added dropwise to a solution of **37** (82 mg, 0.16 mmol) in THF (3.2 mL) at −78 °C under N_2. The reaction mixture was stirred at −78 °C for 2 h, quenched by a slow addition of MeOH (0.25 mL) and vigorously stirred for 10 min at −78 °C. Then a 1 M solution of sodium potassium tartrate (3 mL) was added followed by vigorous stirring at rt for 30 min. It was diluted with H_2O (15 mL), the layers were separated and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. ^1H NMR analysis of the resulting oil showed the presence of **49** as a 88:12 mixture of diastereomers, which were separated by column chromatography (75:25 hexanes/EtOAc) to obtain 64 mg (78% yield) of diastereomerically pure **49** as a colourless oil. R_f (75:25 hexanes/EtOAc) 0.15. $[\alpha]_D^{20}$ −3.4 (*c* 0.9, $CHCl_3$). IR (film) ν 3417 (br), 2957, 2926, 2888, 2854, 1614, 1513, 1469, 1456, 1425, 1247, 1107, 1081, 1035 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76–7.62 (4H, m, Ar*H*), 7.48–7.31 (6H, m, Ar*H*), 7.28–7.18 (2H, m, Ar*H*), 6.92–6.82 (2H, m, Ar*H*), 4.54 (1H, d, *J*=11.2, $PhCH_xH_y$), 4.42 (1H, d, *J*=11.2, $PhCH_xH_y$), 3.90–3.73 (2H, m, 2× C*H*OH), 3.78 (3H, s, *Me*O), 3.73–3.62 (1H, m, C*H*OSi), 3.43 (1H, qd, *J*=6.3, 4.5, C*H*OPMB), 3.30 (2H, br s, 2× O*H*), 1.75 (1H, dt, *J*=14.3, 2.4, CH_xH_y), 1.46 (1H, dt, *J*=14.3, 10.0, CH_xH_y), 1.17 (3H, d, *J*=6.3, *Me*CHOPMB), 1.06 (9H, s, C*Me*$_3$), 1.02 (3H, d, *J*=6.2, *Me*CH). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.1, 135.8 (×2), 134.0, 133.5, 130.6, 129.8, 129.7, 129.2, 127.7, 127.5, 113.8, 77.4, 76.4, 74.4, 72.5, 70.6, 55.2, 33.5, 27.0, 19.3, 18.7, 14.6. HRMS (+ESI): $2MNa^+$, found 1067.5501, $C_{62}H_{84}O_{10}NaSi_2$ requires 1067.5495.

*4.10.2. (2S,3R,5S,6S)-6-(tert-Butyldiphenylsilyloxy)-3,5-O-isopropylidene-2-(p-methoxybenzyloxy)-3,5-heptanediol (**50**).* A solution of **49** (61 mg, 0.12 mmol) and PPTS (cat.) in 1:1 $Me_2C(OMe)_2/CH_2Cl_2$ (1.2 mL) was stirred at rt overnight. Removal of the volatiles and purification of the residue by column chromatography (95:5 hexanes/EtOAc) afforded 54 mg (82% yield) of **50** as a colourless oil. R_f (95:5 hexanes/EtOAc) 0.15. $[\alpha]_D^{20}$ −8.2 (*c* 2.1, $CHCl_3$). IR (film) ν 2988, 2960, 2931, 2891, 2854, 1514, 1427, 1375, 1252, 1111 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76–7.66 (4H, m, Ar*H*), 7.47–7.31 (6H, m, Ar*H*), 7.31–7.22 (2H, m, Ar*H*), 6.92–6.83 (2H, m, Ar*H*), 4.57 (1H, d, *J*=11.4, $PhCH_xH_y$), 4.47 (1H, d, *J*=11.4, $PhCH_xH_y$), 3.89–3.78 (1H, m, C*H*OSi), 3.80 (3H, s, *Me*O), 3.79–3.63 (2H, m, 2× C*H*OH), 3.39 (1H, p, *J*=6.2, C*H*OPMB), 1.69 (1H, dt, *J*=12.7, 2.4, $CH_{eq}H_{ax}$), 1.29–1.13 (1H, m, $CH_{eq}H_{ax}$), 1.31 (3H, s, *Me*CO_2), 1.29 (3H, s, *Me*CO_2), 1.18 (3H, d, *J*=6.2, *Me*CHOPMB), 1.08 (9H, s, C*Me*$_3$), 1.04 (3H, d, *J*=6.4, *Me*CHOSi). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.1, 136.0 (×2), 134.6, 134.5, 130.9, 129.4 (×2), 129.3, 127.4, 127.3, 113.7, 98.4, 77.3, 72.8, 72.4, 71.5, 71.1, 55.2, 29.9, 27.3, 27.0, 19.5 (×2), 18.0, 16.2. HRMS (+ESI): MNH_4^+, found 580.3433, $C_{34}H_{50}O_5NSi$ requires 580.3452.

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