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# Stereoselective titanium-mediated aldol reactions of (*S*)-2-*tert*-butyldimethylsilyloxy-3-pentanone

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**Abstract**—Titanium-mediated aldol reactions based on (*S*)-2-*tert*-butyldimethylsilyloxy-3-pentanone, a lactate-derived chiral ketone, provide the corresponding 2,4-*syn*-4,5-*syn* adducts in high yields and diastereomeric ratios with a wide array of achiral and chiral aldehydes. Furthermore, spectroscopic studies of intermediates involved in the process have permitted to propose a mechanism that accounts for the experimental results.


## 1. Introduction

Aldol reactions involving chiral ketones represent one of the most efficient and versatile methodologies for the stereoselective construction of carbon–carbon bonds.[1] Particularly, pioneering studies by Heathcock et al.[2] and Masamune et al.[3] earlier revealed the synthetic potentiality of α-hydroxy ketones such as **1** and **2** (Fig. 1) and paved the way for the development of a plethora of asymmetric processes based on the reactivity of lithium and boron enolates.[4–8] This chemistry was significantly enriched by Evans discovery that tetrachlorotitanium enolates, generated directly from ketones, participate in highly selective aldol reactions.[9] In the case of ketone **2**, the stereoselectivity of the titanium-mediated aldol reaction was found to be comparable to that reported for the analogous boron-mediated process.[9b] Unfortunately, most of these approaches were bound to chiral ketones containing bulky groups (*tert*-butyl and cyclohexyl in **1** and **2**, respectively, in Fig. 1), which limited their applicability in synthesis. However, Paterson nicely established that the aforementioned steric requirements are not essential and that dicyclohexylborinates from lactate-derived ketones **3** and **4** (Fig. 1) furnish highly stereoselective aldol transformations provided that the hydroxyl protecting group and the enolization procedures are suitably chosen.[10–12] Then, the corresponding aldol adducts can be manipulated to give access to a wide range of molecular architectures present in natural polyoxygenated metabolites.[13] More recently, Denmark has disclosed highly stereoselective aldol processes involving trichlorosilyl enolates from ketone **5** (Fig. 1) and chiral phosphoramides, having proved that the α-chiral center rules the stereochemical outcome of the aldol addition.[14]

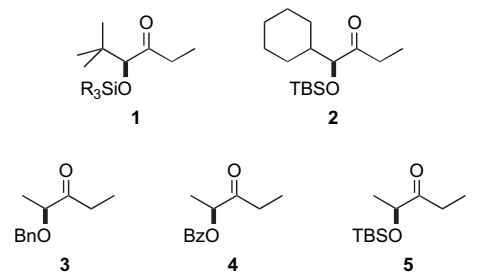


**Figure 1**.

These findings provided us the impetus for launching several years ago a project devoted to the study of aldol reactions based on chiral α-hydroxy ketones[15] and the application of the resulting adducts to the synthesis of polypropionate motifs embedded in natural products. Taking advantage of the high reactivity displayed by titanium enolates, we have developed highly stereoselective aldol reactions based on protected lactate-derived ketones.[16–18] Herein, we disclose an efficient titanium-mediated aldol methodology based on (*S*)-2-*tert*-butyldimethylsilyloxy-3-pentanone (**5**).[19]

## 2. Results and discussion

(*S*)-2-*tert*-Butyldimethylsilyloxy-3-pentanone (**5**) can be prepared through acylation of EtM (M=Li, MgBr) organometallic species with amides derived from commercially available (*S*) lactate esters. Remarkably, enantiomerically pure ketone **5** is routinely prepared in multigram scale

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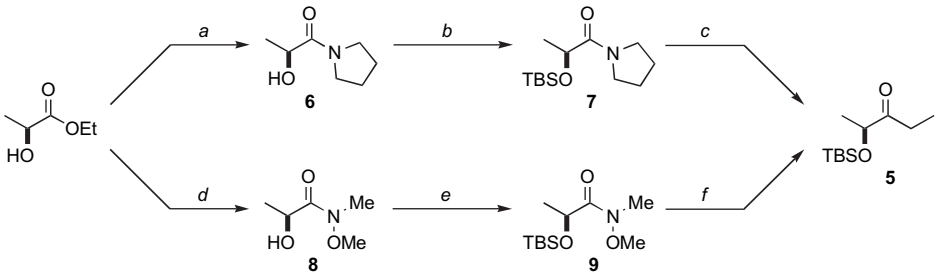



**Scheme 1**. Reagents and conditions: (a) pyrrolidine, rt; (b) TBSCl, $Et_3N$, cat DMAP, rt, THF, 94%; (c) EtLi, −78 °C, THF, 84%; (d) MeONHMe·HCl, *i*-PrMgCl, 76%; (e) TBSCl, $Et_3N$, cat DMAP, rt, THF, 97%; (f) EtMgBr, 0 °C, THF, 92%.

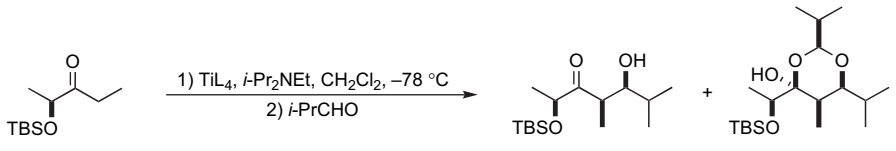
following a synthetic sequence based on *N*-acyl pyrrolidine **6** as shown in Scheme 1. Indeed, the high nucleophilicity of the pyrrolidine permits to obtain quantitatively the hydroxy amide **6** in a free solvent process at rt; then, the crude reaction mixture is submitted to standard silylation conditions and, finally, the resulting silyloxy amide **7** is treated with EtLi to afford the desired ketone **5** in high overall yield (78%).[15c] Alternatively, it can be also prepared in good yields (68%) via Weinreb amide **8**[10] (Scheme 1).[20] Eventually, the corresponding enantiomer, (*R*)-2-*tert*-butyldimethylsilyloxy-3-pentanone (*ent*-**5**), can be likewise obtained from the commercially available (*R*) isobutyl lactate.[15c]

With a straightforward and reliable supply of the required ketone **5** in hand, we began the study of the titanium-mediated aldol reactions with a survey of different Lewis acids. Taking advantage of the experimental procedure reported by Evans, we initially carried out the enolization 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 (1.2 equiv) for 2 h at the same temperature. The results are summarized in Table 1.

As expected, the reactivity of the titanium Lewis acids decreases as the number of alkoxy groups bound to the metal increases, to the point that ketone **5** can be recovered unaltered when Ti(*i*-PrO)$_3$Cl is used (see entry 5 in Table 1). Interestingly, all the other Lewis acids (see entries 1–4 in Table 1) afforded aldol **10a** as a single diastereomer (dr 97:3 by $^1$H NMR), which proved that bulky groups on the ketone are not required to achieve highly diastereoselective processes. We were particularly entrusted with $TiCl_4$ and Ti(*i*-PrO)$Cl_3$, since they could be easily handled and afforded good yields. Further optimization of the process involving both Lewis acids revealed that the enolization as well as the reaction time were pretty fast and could be reduced to 30 min (compare entries 2, 6, and 8 and 3, 7, and 9, respectively).[21] Additionally, we observed the formation of variable amounts (5–10%) of hemiacetal **11a**, which was presumably responsible that some of the abovementioned reactions did not go to completion satisfactorily. Thus, slightly higher and more reproducible yields were obtained using 1.5 equiv of isobutyraldehyde (see entries 10 and 11 in Table 1), although we are aware that good yields can also be achieved with 1.2 equiv.[22]

Next, these experimental procedures were successfully generalized to other aliphatic, aromatic, and α,β-unsaturated aldehydes. As results summarized in Table 2 prove, the corresponding 2,4-*syn*-4,5-*syn* aldols **10** were obtained in high yields and with excellent diastereomeric ratios for a wide array of aliphatic aldehydes, even in the case of sterically undemanding acetaldehyde (see entries 4 and 13 in Table 2). Remarkably, Ti(*i*-PrO)$Cl_3$-mediated aldol reactions afforded slightly better diastereomeric ratios than the corresponding $TiCl_4$ counterparts, being in most cases higher than 95:5.

**Table 1**. Titanium-mediated aldol reaction of ketone **5** with isobutyraldehyde

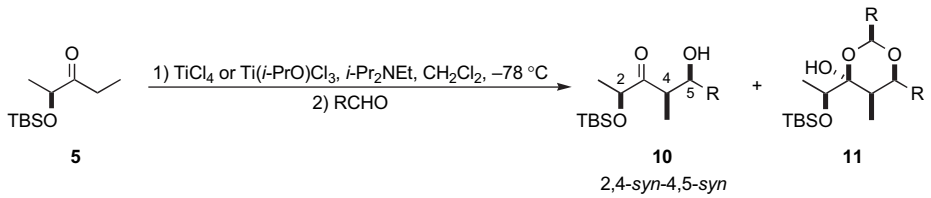



**5** **10a** **11a**

| Entry | Lewis acid | Enolization time (h) | Reaction time (h) | Aldehyde equivalents | Yield of **10** (%)[a] |
|---|---|---|---|---|---|
| 1 | $TiBr_4$ | 1.5 | 2 | 1.2 | 52 (17) |
| 2 | $TiCl_4$ | 1.5 | 2 | 1.2 | 83 (5) |
| 3 | Ti(*i*-PrO)$Cl_3$ | 1.5 | 2 | 1.2 | 76 (14) |
| 4 | Ti(*i*-PrO)$_2Cl_2$ | 1.5 | 2 | 1.2 | 35 (50) |
| 5 | Ti(*i*-PrO)$_3$Cl | 1.5 | 2 | 1.2 | — (90) |
| 6 | $TiCl_4$ | 0.5 | 2 | 1.2 | 80 (<5) |
| 7 | Ti(*i*-PrO)$Cl_3$ | 0.5 | 2 | 1.2 | 74 (15) |
| 8 | $TiCl_4$ | 0.5 | 0.5 | 1.2 | 80 (6) |
| 9 | Ti(*i*-PrO)$Cl_3$ | 0.5 | 0.5 | 1.2 | 80 (10) |
| 10 | $TiCl_4$ | 0.5 | 0.5 | 1.5 | 85 (—) |
| 11 | Ti(*i*-PrO)$Cl_3$ | 0.5 | 0.5 | 1.5 | 85 (<5) |

[a] Isolated yield. In parentheses are the isolated yields of unreacted ketone.

**Table 2**. $TiCl_4$- and Ti(*i*-PrO)$Cl_3$-mediated aldol reactions of ketone **5**




| Entry | Lewis acid | Aldehyde | R | dr[a] | Yield **10** (%)[b] |
|---|---|---|---|---|---|
| 1 | $TiCl_4$ | **a** | $(CH_3)_2CH$ | 97:3 | 85 (82)[c] |
| 2 | $TiCl_4$ | **b** | $(CH_3)_2CHCH_2$ | 95:5 | 81 |
| 3 | $TiCl_4$ | **c** | $CH_3CH_2CH_2$ | 95:5 | 85 |
| 4 | $TiCl_4$ | **d** | $CH_3$ | 91:9 | 58[d] |
| 5 | $TiCl_4$ | **e** | Ph | 93:7[e] | 82 |
| 6 | $TiCl_4$ | **f** | 4-$NO_2$Ph | 95:5[e] | 82 |
| 7 | $TiCl_4$ | **g** | 4-MeOPh | 92:8[e] | 80[f] |
| 8 | $TiCl_4$ | **h** | $H_2C$=$CH(CH_3)$ | 97:3 | 85 (90)[g] |
| 9 | $TiCl_4$ | **i** | (*E*) $CH_3CH$=CH | 96:4 | 80 |
| 10 | Ti(*i*-PrO)$Cl_3$ | **a** | $(CH_3)_2CH$ | 97:3 | 85 (85)[c] |
| 11 | Ti(*i*-PrO)$Cl_3$ | **b** | $(CH_3)_2CHCH_2$ | 97:3 | 78 |
| 12 | Ti(*i*-PrO)$Cl_3$ | **c** | $CH_3CH_2CH_2$ | 96:4 | 86 |
| 13 | Ti(*i*-PrO)$Cl_3$ | **d** | $CH_3$ | 93:7 | 60[d] |
| 14 | Ti(*i*-PrO)$Cl_3$ | **e** | Ph | 93:7[e] | 81 |
| 15 | Ti(*i*-PrO)$Cl_3$ | **f** | 4-$NO_2$Ph | 95:5[e] | 80 |
| 16 | Ti(*i*-PrO)$Cl_3$ | **g** | 4-MeOPh | 92:8[e] | 80[f] |
| 17 | Ti(*i*-PrO)$Cl_3$ | **h** | $H_2C$=$CH(CH_3)$ | 97:3 | 81 |
| 18 | Ti(*i*-PrO)$Cl_3$ | **i** | (*E*) $CH_3CH$=CH | 96:4 | 79 |

[a] Determined by $^1$H NMR.
[b] Isolated yield (dr≥95:5).
[c] Scale=4 mmol.
[d] Thirty percent of hemiacetal **11d** isolated.
[e] Determined by HPLC.
[f] Overall isolated yield.
[g] Scale=3 mmol.

Stereoselectivity was slightly eroded in the case of aromatic aldehydes, especially for the electron rich *p*-methoxybenzaldehyde (**g**), which afforded low diastereomeric ratios (dr 92:8) both with $TiCl_4$ and Ti(*i*-PrO)$Cl_3$. The reasons for this behavior are still unclear. Finally, outstanding diastereoselectivities (dr≥96:4) were also achieved for α,β-unsaturated aldehydes with both Lewis acids.

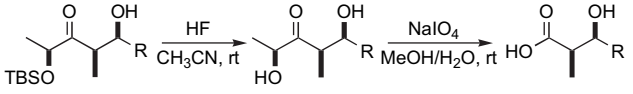
Otherwise, several reactions were easily scaled-up without observing any loss of diastereoselectivity or yield (see entries 1, 8, and 10 in Table 2).

Noteworthy, formation of hemiacetals **11** was routinely observed in the case of aliphatic aldehydes, **a**–**d**. Particularly important was the case of acetaldehyde-derived **11d** (R=Me in Table 2), which turned out to be rather stable and could be isolated more easily than in other cases (see entries 4 and 13 in Table 2).

Relative 4,5-*syn* stereochemistry of aldols **10** was assigned by means of the analysis of diagnostic coupling constants in $^1$H NMR ($^3J_{4,5}$<4.0 Hz) and chemical shifts in $^{13}$C NMR ($\delta_{Me4}$<11 ppm).[23,24] However, absolute stereochemistry required further attention. Hence, removal of protecting groups from representative aldols **10a** and **10e** afforded dihydroxy ketones **12**, which were subsequently converted into the corresponding β-hydroxy carboxylic acids **13** in good overall yield (Table 3). Spectroscopic and physical data of **13** match with those previously reported in the literature and confirmed the configuration assigned to aldols **10**.

The ability of ketone **5** to rule the stereochemical outcome of such substrate-controlled aldol reactions was next challenged in double asymmetric processes[26] confronting titanium enolates from **5** to chiral β- and α-hydroxy aldehydes as **14** (and *ent*-**14**)[27] and **15** (and *ent*-**15**)[28] as shown in Scheme 2. In this context, Evans et al. documented that $TiCl_4$-mediated aldol addition of 2-methyl-3-pentanone to chiral α-methyl-β-hydroxy aldehydes provides the corresponding *anti*-Felkin adducts in moderate stereoselectivity.[29] In addition, preliminary studies carried out in our group proved that the parallel process associated to chiral α-hydroxy aldehyde **15** favors the corresponding Felkin adduct.[16b] Thus, it was not surprising to observe that matched pairs

**Table 3**. Correlation to β-hydroxy acids



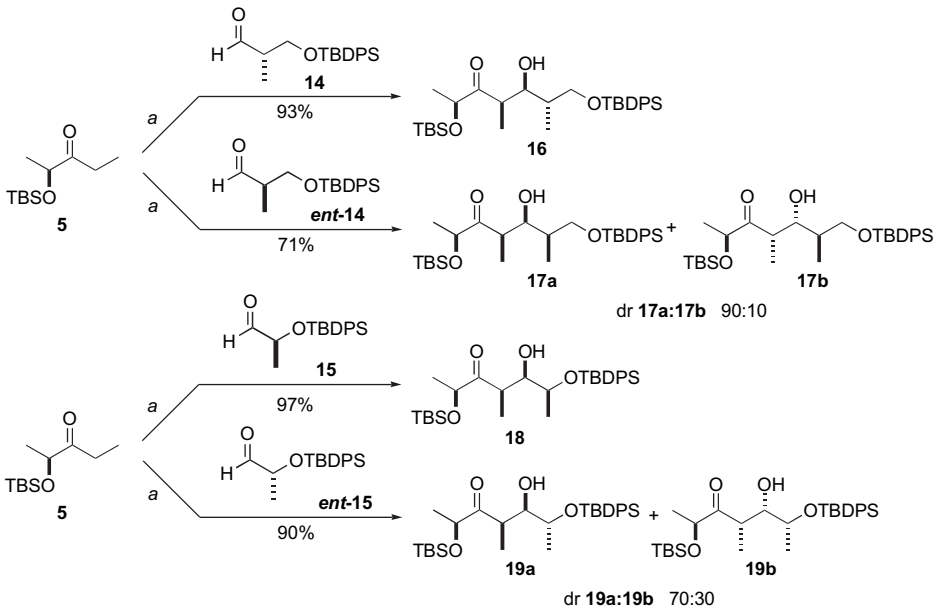

**10a** R = *i*-Pr **10e** R = Ph
**12a** R = *i*-Pr **12e** R = Ph
**13a** R = *i*-Pr **13e** R = Ph

**13a** $[\alpha]_D$=+11.4 (*c* 0.65, $CHCl_3$) Heathcock[2d] $[\alpha]_D$=+9.1 (*c* 2.2, $CHCl_3$); Palomo[25] $[\alpha]_D$=+10.8 (*c* 1.0, $CHCl_3$)

**13e** $[\alpha]_D$=+28.8 (*c* 1.0, $CHCl_3$) Heathcock[2d] $[\alpha]_D$=+28.5 (*c* 1.2, $CHCl_3$); Palomo[25] $[\alpha]_D$=+28.5 (*c* 1.0, $CHCl_3$)

| Entry | Hydroxy acid | R | Overall yield (%)[a] |
|---|---|---|---|
| 1 | **13a** | *i*-Pr | 67 |
| 2 | **13e** | Ph | 82 |

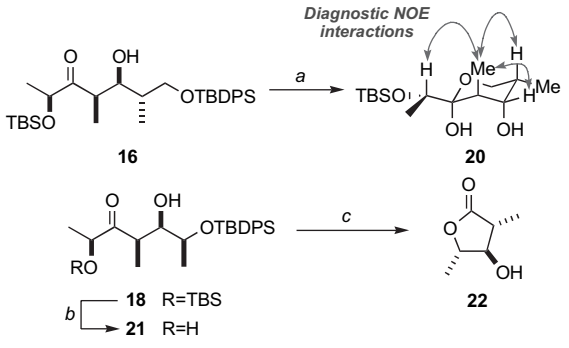
[a] Isolated yield from aldol **10**.




**Scheme 2**. Reagents and conditions: (a) (i) $TiCl_4$, *i*-$Pr_2NEt$, $CH_2Cl_2$, −78 °C; (ii) chiral aldehyde.

involving aldehydes **14** and **15** afforded a single diastereomer in high yields (Scheme 2).[30] For β-hydroxy aldehyde *ent*-**14**, a still synthetically useful mixture (71% yield, dr 90:10) of *syn* diastereomers was obtained irrespective of the Lewis acid ($TiCl_4$ or Ti(*i*-PrO)$Cl_3$) employed. However, ketone **5** hardly overcame the stereochemical bias imparted by the lactate-derived aldehyde *ent*-**15** and a 70:30 mixture of diastereomers was obtained in 90% yield.

The configuration of aldols **16** and **18** was confirmed through the selective removal of the silicon-protecting groups. Indeed, selective cleavage of TBDPS group[31] in **16** afforded hemiacetal **20** (Scheme 3), which was carefully analyzed by 1D and 2D NMR techniques. Alternatively, deprotection of TBS group in **18** provided dihydroxy ketone **21** (Scheme 3), which was, in turn, oxidized with $NaIO_4$ and TBDPS-deprotected to give lactone **22**, whose $^1H$ NMR and $^{13}C$ NMR spectra matched those reported in the literature.[2b] The configuration of major diastereomers in the case of mismatched pairs (**17a** and **19a**) was accounted for the dominant trend due to chiral ketone **5**.



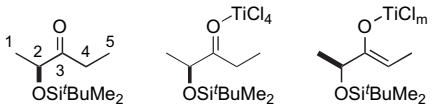

**Scheme 3**. Reagents and conditions: (a) TBAF, AcOH, DMF, rt, 52%; (b) HF, $CH_3CN$, rt, 84%; (c) (i) $NaIO_4$, MeOH/$H_2O$ 2:1, rt; (ii) HF, $CH_3CN$, rt, 45%.

Once established the outline for highly stereoselective reactions, a deeper understanding of the mechanism of the process was considered desirable. Unfortunately, there is a lack of information concerning the structure of titanium enolates. To date, only one crystal X-ray analysis has been reported,[32] theoretical approaches are scarce[33] and spectroscopic studies on titanium enolates in solution[34] have provided a poor knowledge about the aggregation state or the coordination sphere of the titanium.[35] Indeed, it is still unknown if they must be considered as real enolates or alternatively as ate-complexes, the role of the amine or the distribution of ligands around the metal.

Regarding these elusive issues, Evans et al. speculated that ketone-derived titanium enolates exist as aggregated complexes with the amine intimately associated with the enolate, possibly through ion pairing.[9b] This model has been mostly held along mechanistic discussions involving titanium enolates and could be safely applied to our system. However, it was deemed worthwhile to get a more accurate picture of the species implicated in the process. Hence, NMR studies on putative intermediates of the process were carried out in $CD_2Cl_2$ at −78 °C.

In the beginning, it was easy to get both $^1H$ NMR and $^{13}C$ NMR spectra of ketone **5** in $CD_2Cl_2$ at low temperatures, which turned out to be very similar to those previously registered at rt in $CDCl_3$ (for $^1H$ NMR chemical shifts see Table 4). Unfortunately, subsequent study of the $TiCl_4$–ketone complex **23** proved troublesome because silicon-protecting group resulted to be too sensitive to the Lewis acid. Finally, careful addition of a solution of $TiCl_4$ to a stock solution of ketone **5** at −78 °C and quick analysis of the resulting mixture allowed us to observe significant downfield shifts for nuclei close to the carbonyl and the ether groups (see Table 4) and a common peak broadening, which suggests a dynamic behavior. At last, $^1H$ NMR spectra of the ensuing enolate showed a main set of broad signals and

**Table 4**. $^1$H NMR (300 MHz) chemical shifts ($CD_2Cl_2$, −78 °C) of ketone **5** and intermediates **23** and **24**



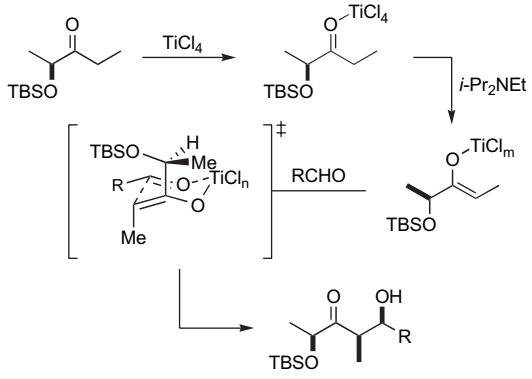

**5** **23** **24**

| Entry | Nucleus | $\delta$ in **5**[a] | $\delta$ in **23**[a] | $\delta$ in **24**[a] |
|---|---|---|---|---|
| 1 | H1 | 1.17 | 1.40 | 1.35 |
| 2 | H2 | 4.07 | 4.90 | 4.60 |
| 3 | H4 | 2.51, 2.63 | 3.00 | 5.30 |
| 4 | H5 | 0.87 | 1.05 | 1.95 |
| 5 | Si–Me | −0.01 | 0.10 | −0.01 |
| 6 | Si–*t*Bu | 0.82 | 0.87 | 0.81 |

[a] Chemical shifts ($\delta$) are quoted in parts per million referenced to $CHDCl_2$ ($\delta$ 5.31).

a close inspection of its 2D NOESY NMR revealed cross-peaks between C═CH and OTBS group. Hence, these evidences support a *Z* geometry and an antiperiplanar arrangement of both C–O bonds for the enolate **24** (see Table 4 and Scheme 4).

These pieces of evidence and the models currently accepted permit to propose the mechanism for the process represented in Scheme 4. As shown, enolization of a chelated $TiCl_4$–ketone complex provides the corresponding *Z*-enolate, which evolves through a cyclic six-membered transition state. In such scenario, the antiperiplanar distribution of both TBSO–C and C–OTi bonds would act as the key element that determines the stereochemical outcome of the reaction since the preferred chair transition state places the less sterically demanding substituent (H vs Me) of the Cα stereocenter pointing toward the inside of the ring, as it has been previously proposed for similar systems.[2d,3b,10,36]




**Scheme 4**.

This mechanism is consistent with the stereochemical outcome of reactions involving both achiral and chiral aldehydes. Indeed, chiral α-methyl-β-hydroxy aldehydes show the usual *anti*-Felkin bias according to the model established by Roush.[37] Likewise, α-hydroxy aldehydes afford the expected Felkin adducts, although in this case the Cornforth paradigm is the theoretical model[38] that more accurately describes the asymmetric induction in aldol additions to α-alkoxy aldehydes.[39,40]

## 3. Conclusions

In summary, we have proved that titanium enolates from lactate-derived chiral ketone **5** can be easily obtained by direct enolization with $TiCl_4$/*i*-$Pr_2$NEt and Ti(*i*-PrO)$Cl_3$/*i*-$Pr_2$NEt. Furthermore, they participate in highly stereoselective aldol processes with a wide scope of achiral and chiral aldehydes that afford the corresponding 2,4-*syn*-4,5-*syn* diastereomers in good yields irrespective of the titanium Lewis acid used in the enolization. Finally, spectroscopic studies of the intermediates involved in this process have permitted to propose a mechanism that accounts for the experimental results.

## 4. Experimental

### 4.1. General

Melting points were taken on an Electrothermal apparatus and have not been corrected. Specific rotations were determined at 20 °C on a Perkin–Elmer 241 MC polarimeter. IR spectra were recorded on either a Perkin–Elmer 681 or a Nicolet 510 FT spectrometer and only the more representative frequencies ($cm^{-1}$) are reported. $^1$H NMR (300 MHz) and $^{13}$C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus 300 spectrometer; $^1$H NMR (400 MHz) and $^{13}$C NMR (100.6 MHz) spectra were recorded on a Varian Mercury; $^1$H NMR (500 MHz) spectra were recorded on a Varian Unity Inova 500 spectrometer; chemical shifts ($\delta$) are quoted in parts per million and referenced to internal TMS for $^1$H NMR and $CDCl_3$ ($\delta$ 77.0) for $^{13}$C NMR; data are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; hep, heptuplet; m, multiplet; br, broad; coupling constants (*J*) are quoted in hertz; where appropriate, 2D techniques were also used to assist in structural elucidation. Low resolution chemical ionization mass spectra (MS) were recorded on an HP-5988 A spectrometer. High resolution mass spectra (HRMS) were obtained from the Centro de Apoio Cientifico Tecnoloxico a Investigacion (C.A.C.T.I.), Universidad de Vigo. HPLC was carried out with a BGY 126 (250×4 mm) column [silica gel Spherisorb S3W] with a 0.9 mL $min^{-1}$ flux. Flash chromatography was performed on SDS silica gel (35–70 μm). Analytical thin-layer chromatography was carried out on Merck Kieselgel 60 $F_{254}$ plates. The following solvents and reagents were purified and dried according to the standard procedures: $CH_2Cl_2$, THF, $Et_2O$, DMF, *i*-$Pr_2$NEt. All other reagents were used as received.

### 4.2. Preparation of (*S*)-2-*tert*-butyldimethylsilyloxy-3-pentanone (5)

**4.2.1. (*S*)-2-*tert*-Butyldimethylsilyloxy-*N*-methoxy-*N*-methylpropanamide (9).** A solution of TBSCl (2.56 g, 17.0 mmol) in THF (5+1 mL) was added via canula to a solution of **8**[10] (1.51 g, 11.3 mmol), $Et_3N$ (3.9 mL, 27.8 mmol) and a catalytic amount of DMAP in THF (10 mL) at 0 °C under $N_2$. The resulting mixture was stirred at 0 °C for 10 min at rt for two days. It was then diluted with $Et_2O$ (150 mL), washed with 1 M HCl (50 mL), satd $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. The resulting oil was purified by flash chromatography (from hexanes/EtOAc 90:10

to 60:40), which afforded 2.72 g (11.0 mmol, 97%) of (*S*)-2-*tert*-butyldimethylsilyloxy-*N*-methoxy-*N*-methylpropanamide (**9**). Colorless oil; $R_f$=0.65 (hexanes/EtOAc 60:40); $[\alpha]_D$ −24.6 (*c* 1.0, $CHCl_3$); IR (film): *ν* 2956, 2933, 1686; $^1$H NMR ($CDCl_3$, 300 MHz) *δ* 4.68 (1H, q, *J*=6.6, C*H*OTBS), 3.70 (3H, s, OC$H_3$), 3.21 (3H, br s, NC$H_3$), 1.33 (3H, d, *J*=6.6, C$H_3$CHOTBS), 0.91 (9H, s, SiC(C$H_3$)$_3$), 0.11 (3H, s, SiC$H_3$), 0.08 (3H, s, SiC$H_3$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) *δ* 66.6 (br), 61.2, 32.8 (br), 25.8, 20.9, 18.3, −4.7, −5.0.

**4.2.2. (*S*)-2-*tert*-Butyldimethylsilyloxy-3-pentanone (5).** A 2 M solution of EtMgCl (10.9 mL, 21.8 mmol) in $Et_2O$ was added dropwise to a solution of **9** (2.69 g, 10.9 mmol) in THF (140 mL) at 0 °C under $N_2$ and the resulting mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of satd $NH_4Cl$ (80 mL). The organic layer was washed with satd $NH_4Cl$ (50 mL) and $H_2O$ (50 mL). The aqueous layers were extracted with $Et_2O$ (2×100 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated carefully (*caution: concentration in vacuo has to be carried out carefully in order to prevent losses of product*). The resulting oil was purified by flash chromatography (hexanes/$Et_2O$ 90:10), which afforded 2.16 g (10.0 mmol, 92% yield) of (*S*)-2-*tert*-butyldimethylsilyloxy-3-pentanone (**5**).[15c]

### 4.3. General procedure of titanium-mediated aldol reactions from ketone 5

**4.3.1. Using $TiCl_4$.** Neat $TiCl_4$ (0.12 mL, 1.1 mmol) is added slowly to a solution of ketone **5** (216 mg, 1.0 mmol) in $CH_2Cl_2$ (5 mL) at −78 °C under $N_2$. The resulting yellow mixture is stirred for 3–4 min and *i*-$Pr_2$NEt (0.19 mL, 1.1 mmol) is added dropwise. The resulting dark red solution is stirred for 30 min at −78 °C and, after the dropwise addition of freshly distilled aldehyde (1.5 equiv), stirring is continued for 30 min at −78 °C. The reaction is quenched by the addition of satd $NH_4Cl$ (5 mL) and vigorously stirred at rt. The mixture is diluted with $Et_2O$, washed with $H_2O$, satd $NaHCO_3$, and brine. The aqueous phases are extracted with $Et_2O$, and the combined organic extracts are dried ($MgSO_4$) and concentrated. The resulting oil is analyzed by $^1$H NMR or HPLC and purified by flash chromatography (hexanes/EtOAc or $CH_2Cl_2$).

*Note—p-nitrobenzaldehyde was added as a solution in $CH_2Cl_2$ (0.5 mL+0.5 mL) using 4 mL of solvent for the enolization. Methacrolein was used as received.*

**4.3.2. Using Ti(*i*-PrO)$Cl_3$.** Freshly distilled Ti(*i*-PrO)$_4$ (83 μL, 0.28 mmol) is added dropwise to a solution of $TiCl_4$ (92 μL, 0.84 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C under $N_2$. The resulting yellow mixture is stirred for 10 min at 0 °C, diluted with $CH_2Cl_2$ (1 mL) and stirred for 10 min at rt. Then, the ensuing colorless solution is added dropwise (it is rinsed with 2×0.5 mL) via canula for 10–15 min to a solution of ketone **5** (216 mg, 1.0 mmol) in $CH_2Cl_2$ (2 mL) at −78 °C under $N_2$, followed by *i*-$Pr_2$NEt (0.19 mL, 1.1 mmol). The resulting dark red solution is stirred for 30 min at −78 °C and, after the dropwise addition of freshly distilled aldehyde (1.5 equiv), stirring is continued for 30 min at −78 °C. The reaction mixture is quenched and worked-up as in the previous case.

**4.3.3. (2*S*,4*R*,5*S*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4,6-dimethyl-3-heptanone (10a).** Colorless oil; $R_f$=0.2 (hexanes/EtOAc 9:1); $[\alpha]_D$ +24.7 (*c* 0.89, $CHCl_3$); IR (film): *ν* 3530 (br), 1702; $^1$H NMR ($CDCl_3$, 500 MHz) *δ* 4.19 (1H, q, *J*=7.0, C*H*OTBS), 3.42 (1H, dd, *J*=8.8, *J*=2.4, C*H*OH), 3.32 (1H, qd, *J*=7.2, *J*=2.4, COC*H*CH$_3$CHOH), 1.72–1.62 (1H, m, C*H*(CH$_3$)$_2$), 1.32 (3H, d, *J*=7.0, C$H_3$CHOTBS), 1.11 (3H, d, *J*=7.2, COCHC$H_3$CHOH), 1.00 (3H, d, *J*=6.6, C$H_3$), 0.90 (9H, s, SiC(C$H_3$)$_3$), 0.82 (3H, d, *J*=6.8, C$H_3$), 0.07 (3H, s, SiC$H_3$), 0.06 (3H, s, SiC$H_3$); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) *δ* 219.8 (C), 76.1 (CH), 74.6 (CH), 41.3 (CH), 30.4 (CH), 25.7 (CH$_3$), 21.4 (CH$_3$), 19.4 (CH$_3$), 18.8 (CH$_3$), 18.0 (C), 9.3 (CH$_3$), −4.7 (CH$_3$), −5.0 (CH$_3$); HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{15}H_{33}O_3Si$: 289.2207; found: 289.2199.

**4.3.4. (2*S*,4*R*,5*S*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4,7-dimethyl-3-octanone (10b).** Colorless oil; $R_f$=0.3 (hexanes/EtOAc 9:1); $[\alpha]_D$ +2.7 (*c* 2.1, $CHCl_3$); IR (film): *ν* 3500 (br), 1720; $^1$H NMR ($CDCl_3$, 500 MHz) *δ* 4.21 (1H, q, *J*=6.8, C*H*OTBS), 3.94 (1H, ddd, *J*=9.3, *J*=4.1, *J*=2.9, C*H*OH), 3.08 (1H, qd, *J*=7.2, *J*=2.9, COC*H*CH$_3$CHOH), 1.85–1.70 (1H, m, C*H*(CH$_3$)$_2$), 1.55–1.42 (1H, m, C$H_x$H$_y$), 1.34 (3H, d, *J*=6.8, C$H_3$CHOTBS), 1.14 (3H, d, *J*=7.2, COCHC$H_3$CHOH), 1.15–1.00 (1H, m, CH$_x$$H_y$), 0.92 (9H, s, SiC(C$H_3$)$_3$), 0.92 (3H, d, *J*=6.8, C$H_3$), 0.91 (3H, d, *J*=6.5, C$H_3$), 0.10 (3H, s, SiC$H_3$), 0.09 (3H, s, SiC$H_3$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) *δ* 219.2, 74.6, 68.8, 44.5, 43.1, 25.7, 24.5, 23.4, 22.0, 21.3, 18.0, 10.1, −4.6, −5.0; HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{16}H_{35}O_3Si$: 303.2355; found: 303.2362.

**4.3.5. (2*S*,4*R*,5*S*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4-methyl-3-octanone (10c).** Colorless oil; $R_f$= 0.2 (hexanes/EtOAc 9:1); $[\alpha]_D$ +9.2 (*c* 1.35, $CHCl_3$); IR (film): *ν* 3475 (br), 1711; $^1$H NMR ($CDCl_3$, 500 MHz) *δ* 4.19 (1H, q, *J*=6.9, C*H*OTBS), 3.85–3.80 (1H, m, C*H*OH), 3.10 (1H, qd, *J*=7.2, *J*=2.8, COC*H*CH$_3$CHOH), 1.55–1.40 (2H, m, CHOHC$H_2$), 1.35–1.20 (2H, m, C$H_2$CH$_3$), 1.31 (3H, d, *J*=6.9, C$H_3$CHOTBS), 1.11 (3H, d, *J*=7.2, COCHC$H_3$CHOH), 0.91 (3H, t, *J*=7.2, CH$_2$C$H_3$), 0.90 (9H, s, SiC(C$H_3$)$_3$), 0.07 (6H, s, Si(C$H_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) *δ* 219.1, 74.5, 70.6, 44.1, 36.1, 25.7, 21.3, 19.2, 18.0, 14.0, 9.9, −4.7, −5.0; HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{15}H_{33}O_3Si$: 289.2199; found: 289.2195.

**4.3.6. (2*S*,4*R*,5*S*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4-methyl-3-hexanone (10d).** Colorless oil; $R_f$= 0.15 (hexanes/EtOAc 9:1); $[\alpha]_D$ +16.8 (*c* 1.0, $CHCl_3$); IR (film): *ν* 3462 (br), 1713; $^1$H NMR ($CDCl_3$, 300 MHz) *δ* 4.21 (1H, q, *J*=6.9, C*H*OTBS), 4.06 (1H, qd, *J*=6.4, *J*=3.4, C*H*OH), 3.08 (1H, qd, *J*=7.2, *J*=3.4, COC*H*CHOH), 1.34 (3H, d, *J*=6.9, C$H_3$CHOTBS), 1.15 (3H, d, *J*=7.2, COCHC$H_3$CHOH), 1.15 (3H, d, *J*=6.4, CHOHC$H_3$), 0.92 (9H, s, SiC(C$H_3$)$_3$), 0.10 (3H, s, SiC$H_3$), 0.09 (3H, s, SiC$H_3$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) *δ* 218.6, 74.5, 67.1, 45.5, 25.6, 21.1, 20.0, 18.0, 10.2, −4.7, −5.1; HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{13}H_{29}O_3Si$: 261.1886; found 261.1892.

**4.3.7. (1*R*,2*R*,4*S*)-4-*tert*-Butyldimethylsilyloxy-1-hydroxy-2-methyl-1-phenyl-3-pentanone (10e).** Colorless oil; $R_f$=0.15 (hexanes/EtOAc 9:1); HPLC (hexanes/*i*-PrOH 99:1) $t_R$=5.2 min (minor diastereomer, $t_R$=5.6 min); $[\alpha]_D$ +4.2 (*c* 1.0, $CHCl_3$); IR (film): $\nu$ 3500 (br), 1713; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.34–7.30 (4H, m, Ar*H*), 7.26–7.21 (1H, m, Ar*H*), 5.03 (1H, d, *J*=3.7, C*H*OH), 4.14 (1H, q, *J*=6.9, C*H*OTBS), 3.37 (1H, qd, *J*=7.2, *J*=3.7, COC*H*$CH_3$CHOH), 1.27 (3H, d, *J*=6.9, C*H*$_3$CHOTBS), 1.05 (3H, d, *J*=7.2, COCHC*H*$_3$CHOH), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.06 (3H, s, SiC*H*$_3$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 218.7, 141.7, 128.2, 127.2, 125.9, 74.6, 72.8, 46.9, 25.7, 21.0, 18.0, 10.4, −4.7, −5.0; HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{18}H_{31}O_3Si$: 323.2042; found: 323.2045.

**4.3.8. (1*R*,2*R*,4*S*)-4-*tert*-Butyldimethylsilyloxy-1-hydroxy-2-methyl-1-(4-nitrophenyl)-3-pentanone (10f).** Colorless oil; $R_f$=0.30 ($CH_2Cl_2$); HPLC (hexanes/EtOAc 97.5:2.5) $t_R$=35.3 min (minor diastereomer, $t_R$=50.1 min); $[\alpha]_D$ −0.6 (*c* 1.1, $CHCl_3$); IR (film): $\nu$ 3512 (br), 1710, 1524, 1349; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.25–8.15 (2H, m, Ar*H*), 7.55–7.45 (2H, m, Ar*H*), 5.17 (1H, br s, C*H*OH), 4.23 (1H, q, *J*=6.9, C*H*OTBS), 3.41 (1H, qd, *J*=7.2, *J*=2.9, COC*H*$CH_3$CHOH), 1.35 (3H, d, *J*=6.9, C*H*$_3$CHOTBS), 1.03 (3H, d, *J*=7.2, COCHC*H*$_3$CHOH), 0.92 (9H, s, SiC(C*H*$_3$)$_3$), 0.11 (6H, s, Si(C*H*$_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 218.8, 149.1, 147.2, 126.7, 123.5, 74.7, 71.9, 46.3, 25.7, 21.4, 18.0, 9.8, −4.6, −5.0; HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{18}H_{30}NO_5Si$: 368.1893; found: 368.1882.

**4.3.9. (1*R*,2*R*,4*S*)-4-*tert*-Butyldimethylsilyloxy-1-hydroxy-1-(4-methoxyphenyl)-2-methyl-3-pentanone (10g).** Colorless oil; $R_f$=0.25 ($CH_2Cl_2$); $[\alpha]_D$ +1.7 (*c* 1.0, $CHCl_3$); HPLC (hexanes/*i*-PrOH 99:1) $t_R$=6.5 min (minor diastereomer, $t_R$=8.0 min); IR (film): $\nu$ 3504 (br), 1713; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.28–7.20 (2H, m, Ar*H*), 6.92–6.84 (2H, m, Ar*H*), 4.99 (1H, dd, *J*=4.0, *J*=1.8, C*H*OH), 4.13 (1H, q, *J*=6.8, C*H*OTBS), 3.80 (3H, s, OC*H*$_3$), 3.35 (1H, qd, *J*=7.1, *J*=4.0, COC*H*$CH_3$CHOH), 1.27 (3H, d, *J*=6.8, C*H*$_3$CHOTBS), 1.08 (3H, d, *J*=7.1, COCHC*H*$_3$CHOH), 0.92 (9H, s, SiC(C*H*$_3$)$_3$), 0.09 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 218.5, 158.8, 134.0, 127.1, 113.6, 74.6, 72.6, 55.2, 47.1, 25.7, 20.9, 18.0, 10.8, −4.7, −5.0; HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{19}H_{33}O_4Si$: 353.2148; found: 353.2141.

**4.3.10. (2*S*,4*R*,5*R*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4,6-dimethyl-6-hepten-3-one (10h).** Colorless oil; $R_f$=0.1 (hexanes/EtOAc 94:6); $[\alpha]_D$ +12.4 (*c* 1.0, $CHCl_3$); IR (film): $\nu$ 3500 (br), 1702, 1653; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 5.12–5.09 (1H, m, C=C*H*$_x$H$_y$), 4.95–4.93 (1H, m, C=CH$_x$*H*$_y$), 4.32 (1H, br s, C*H*OH), 4.21 (1H, q, *J*=6.9, C*H*OTBS), 3.30 (1H, qd, *J*=7.2, *J*=2.8, COC*H*$CH_3$CHOH), 1.67–1.65 (3H, m, C*H*$_3$C=CH$_2$), 1.28 (3H, d, *J*=6.9, C*H*$_3$CHOTBS), 1.06 (3H, d, *J*=7.2, C*H*$_3$CHOTBS), 0.91 (9H, s, SiC(C*H*$_3$)$_3$), 0.08 (6H, s, Si(C*H*$_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 219.2, 143.2, 111.8, 74.6, 73.2, 41.8, 25.7, 21.3, 19.6, 18.0, 9.6, −4.6, −5.0; HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{15}H_{31}O_3Si$: 287.2042; found: 287.2035.

**4.3.11. (2*S*,4*R*,5*S*,6*E*)-2-*tert*-Butyldimethylsilyloxy-5-hydroxy-4-methyl-6-octen-3-one (10i).** Yellowish oil; $R_f$=0.2 (hexanes/EtOAc 9:1); $[\alpha]_D$ −6.3 (*c* 1.3, $CHCl_3$); IR (film): $\nu$ 3475 (br), 1709, 1640; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 5.72 (1H, dqd, *J*=15.7, *J*=6.5, *J*=1.2, HC=C*H*$CH_3$), 5.44 (1H, ddq, *J*=15.7, *J*=6.5, *J*=1.7, *H*C=CHC*H*$_3$), 4.36–4.32 (1H, m, C*H*OH), 4.21 (1H, q, *J*=6.9, C*H*OTBS), 3.19 (1H, qd, *J*=7.2, *J*=3.8, COC*H*$CH_3$CHOH), 1.70 (3H, ddd, *J*=6.5, *J*=1.7, *J*=0.9, HC=CHC*H*$_3$), 1.30 (3H, d, *J*=6.9, C*H*$_3$CHOTBS), 1.11 (3H, d, *J*=7.2, COCHC*H*$_3$CHOH), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 0.07 (6H, s, Si(C*H*$_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 217.7, 130.7, 127.7, 74.6, 72.2, 45.2, 25.7, 21.0, 18.0, 17.7, 11.1, −4.6, −5.0; HRMS (+FAB): *m*/*z* calcd for $[M+H]^+$ $C_{15}H_{31}O_3Si$: 287.2042; found: 287.2050.

**4.3.12. Hemiacetal from *i*-PrCHO (11a).** Colorless oil; $R_f$=0.6 (hexanes/EtOAc 9:1); $[\alpha]_D$ −22.7 (*c* 0.6, $CHCl_3$); IR (film): $\nu$ 3525, 2957, 2929; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 4.84 (1H, d, *J*=4.5, OCHO), 3.83 (1H, q, *J*=6.3, C*H*OTBS), 3.64 (1H, s, OH), 3.59 (1H, dd, *J*=9.7, *J*=2.0, OC*H*CH(CH$_3$)$_2$), 1.85–1.60 (3H, m, C*H*CH$_3$ and 2×C*H*(CH$_3$)$_2$), 1.13 (3H, d, *J*=6.0, C*H*$_3$), 1.03 (3H, d, *J*=6.3, C*H*$_3$), 0.98 (3H, d, *J*=6.9, C*H*$_3$), 0.96 (3H, d, *J*=6.9, C*H*$_3$), 0.93 (9H, s, SiC(C*H*$_3$)$_3$), 0.89 (3H, d, *J*=6.6, C*H*$_3$), 0.83 (3H, d, *J*=6.9, C*H*$_3$), 0.14 (3H, s, SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 98.5, 98.3, 80.1, 71.2, 33.7, 32.4, 28.7, 25.8, 19.8, 18.1, 17.3, 17.2, 16.9, 16.4, 6.9, −4.6, −4.9.

**4.3.13. Hemiacetal from $CH_3CHO$ (11d).** Colorless oil; $R_f$=0.5 (hexanes/EtOAc 9:1); $[\alpha]_D$ −22.9 (*c* 1.3, $CHCl_3$); IR (film): $\nu$ 3527, 2933; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 5.27 (1H, q, *J*=5.2, OC*H*O), 4.34 (1H, qd, *J*=6.6, *J*=2.1, C(OH)–CHC*H*CH$_3$), 3.78 (1H, q, *J*=6.3, C*H*OTBS), 3.63 (1H, s, O*H*), 1.40 (1H, qd, *J*=6.8, *J*=2.1, C(OH)C*H*(CH$_3$)CH), 1.26 (3H, d, *J*=5.2, OCH(C*H*$_3$)O), 1.13 (3H, d, *J*=6.6, C(OH)CHCHC*H*$_3$), 1.07 (3H, d, *J*=6.3, C*H*$_3$CHOTBS), 0.90 (3H, d, *J*=6.8, C(OH)CH(C*H*$_3$)CH), 0.89 (9H, s, SiC(C*H*$_3$)$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.07 (3H, s, SiC*H*$_3$); $^1$H NMR ($C_6D_6$, 400 MHz) $\delta$ 5.41 (1H, q, *J*=5.2, OC*H*O), 4.50 (1H, qd, *J*=6.5, *J*=2.2, C(OH)CHC*H*CH$_3$), 3.79 (1H, q, *J*=6.2, C*H*OTBS), 3.64 (1H, s, O*H*), 1.34 (3H, d, *J*=5.2, OCH(C*H*$_3$)O), 1.31 (1H, qd, *J*=6.8, *J*=2.2, C(OH)–C*H*(CH$_3$)CH), 1.04 (3H, d, *J*=6.5, C(OH)CHCHC*H*$_3$), 1.01 (3H, d, *J*=6.2, C*H*$_3$CHOTBS), 0.94 (9H, s, SiC(C*H*$_3$)$_3$), 0.83 (3H, d, *J*=6.8, C(OH)CH(C*H*$_3$)CH), 0.09 (3H, s, SiC*H*$_3$), 0.07 (3H, s, SiC*H*$_3$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 98.4, 91.9, 71.2, 70.1, 36.7, 25.8, 20.7, 18.2, 18.0, 16.7, 6.7, −4.6, −5.1.

### 4.4. General procedure for TBS removal

A 48% aq solution of HF (3 equiv) is added dropwise to a 0.2 M solution of aldol **10** in $CH_3CN$ at rt. The reaction mixture is stirred for 1 h and diluted with $CH_2Cl_2$. The organic layer is washed with satd $NaHCO_3$, dried ($MgSO_4$) and concentrated. The resulting oil is purified by flash chromatography (hexanes/EtOAc), which affords dihydroxy ketones **12** in 74–87% yield.

**4.4.1. (2*S*,4*R*,5*S*)-2,5-Dihydroxy-4,6-dimethyl-3-heptanone (12a).** Yield: 74%. Colorless oil; $R_f$=0.25 (hexanes/

EtOAc 60:40); $[\alpha]_D$ +69.9 (*c* 1.5, $CHCl_3$); IR (film): $\nu$ 3438 (br), 2967, 1708; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 4.45 (1H, q, *J*=7.0, $CH_3CHOH$), 3.58 (1H, dd, *J*=8.0, *J*=3.2, $COCHCHOH$), 2.99 (1H, qd, *J*=7.2, *J*=3.2, $COCHCHOH$), 1.71 (1H, dhep, *J*=8.0, *J*=6.6, $CH(CH_3)_2$), 1.42 (3H, d, *J*=7.0, $CH_3CHOH$), 1.19 (3H, d, *J*=7.2, $COCHCH_3$), 1.03 (3H, d, *J*=6.6, $CH(CH_3)_2$), 0.90 (3H, d, *J*=6.6, $CH(CH_3)_2$); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 217.7, 75.7, 71.2, 42.8, 30.4, 19.9, 19.1, 18.7, 10.4; MS (CI–$NH_3$) *m*/*z*: $[M+NH_4]^+$=192 (100).

**4.4.2. (1*R*,2*R*,4*S*)-1,4-Dihydroxy-2-methyl-1-phenyl-3-pentanone (12e).** Yield: 87%. Colorless oil; $R_f$=0.20 (hexanes/EtOAc 60:40); $[\alpha]_D$ +42.1 (*c* 1.1, $CHCl_3$); IR (film): $\nu$ 3409 (br), 3063, 2979, 1710; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.40–7.20 (5H, m, Ar*H*), 5.06 (1H, dd, *J*=5.4, *J*=2.2, $CHOHPh$), 4.32 (1H, qd, *J*=7.1, *J*=5.1, $CH_3CHOH$), 3.35 (1H, d, *J*=5.1, $CH_3CHOH$), 3.07 (1H, qd, *J*=7.1, *J*=5.4, $COCHCH_3CHOH$), 2.84 (1H, br s, $CHOHPh$), 1.17 (3H, d, *J*=7.1, $COCHCH_3CHOH$), 1.09 (3H, d, *J*=7.1, $CH_3CHOH$); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 216.3, 141.7, 128.3, 127.8, 126.1, 73.2, 71.5, 48.6, 19.1, 12.3; MS (CI–$NH_3$) *m*/*z*: $[M+NH_4]^+$=226 (100).

### 4.5. General procedure for oxidation of α-hydroxy ketones

A mixture of dihydroxy ketone **12** (1 mmol) and $NaIO_4$ (1.46 g, 10 mmol) in 2:1 MeOH/$H_2O$ (10 mL) is stirred for 1 h at rt. It is diluted with $Et_2O$ (10 mL), cooled to 0 °C, and 1 M HCl is slowly added to reach pH 1. The mixture is partitioned with $Et_2O$ (10 mL) and $H_2O$ (10 mL). The organic layer is separated and the aqueous layer is thoroughly extracted with $Et_2O$ (4×10 mL). The combined ethereal extracts are dried ($MgSO_4$) and concentrated. The resulting oil is purified by flash chromatography ($CH_2Cl_2$/MeOH 95:5), which affords hydroxy acids **13** in 90–95% yield.

**4.5.1. (2*R*,3*S*)-3-Hydroxy-2,4-dimethylpentanoic acid (13a).** Yield: 90%. Viscous colorless oil; $R_f$=0.10 ($CH_2Cl_2$/MeOH 95:5); $[\alpha]_D$ +11.4 (*c* 0.65, $CHCl_3$) [lit.[2d] $[\alpha]_D$ +9.1 (*c* 2.2, $CHCl_3$); lit.[25] $[\alpha]_D$ +10.8 (*c* 1.0, $CHCl_3$)]; IR (film): $\nu$ 3500–2750 (br), 1711; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 6.40 (2H, br s, 2×O*H*), 3.64 (1H, dd, *J*=8.1, *J*=3.6, C*H*OH), 2.71 (1H, qd, *J*=7.1, *J*=3.6, HOOCC*H*), 1.73 (1H, dhep, *J*=8.1, *J*=6.7, $CH(CH_3)_2$), 1.21 (3H, d, *J*=7.1, $HOOCCHCH_3$), 1.02 (3H, d, *J*=6.7, $CH_3CHCH_3$), 0.89 (3H, d, *J*=6.7, $CH_3CHCH_3$); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 181.6, 76.9, 41.8, 30.6, 19.0, 18.7, 9.7; MS (CI–$NH_3$) *m*/*z*: $[M+NH_4]^+$=164 (100), $[M+H]^+$=147 (16).

**4.5.2. (2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropanoic acid (13e).** Yield: 95%. White solid; mp=76–77 °C [lit.[25] mp=78–79 °C]; $R_f$=0.10 ($CH_2Cl_2$/MeOH 95:5); $[\alpha]_D$ +28.8 (*c* 1.0, $CHCl_3$) [lit.[2d] $[\alpha]_D$ +28.5 (*c* 1.27, $CHCl_3$); lit.[25] $[\alpha]_D$ +28.5 (*c* 1.0, $CHCl_3$)]; IR (film): $\nu$ 3500–2750 (br), 1708; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.40–7.20 (5H, m, Ar*H*), 6.40 (2H, br s, 2×O*H*), 5.17 (1H, d, *J*=3.9, C*H*OH), 2.84 (1H, qd, *J*=7.1, *J*=3.9, $COCHCH_3$), 1.15 (3H, d, *J*=7.1, $COCHCH_3$); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 180.9, 141.0, 128.4, 127.7, 125.9, 73.4, 46.2, 10.3; MS (CI–$NH_3$) *m*/*z*: $[M+NH_4]^+$=198 (100).

### 4.6. Spectroscopic data for aldol adducts from chiral aldehydes

**4.6.1. (2*S*,4*R*,5*S*,6*S*)-2-*tert*-Butyldimethylsilyloxy-7-*tert*-butyldiphenylsilyloxy-5-hydroxy-4,6-dimethyl-3-heptanone (16).** Yellowish oil; $R_f$=0.35 (hexanes/EtOAc 90:10); $[\alpha]_D$ +10.4 (*c* 1.05, $CHCl_3$); IR (film): $\nu$ 3516 (br), 1702; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.70–7.65 (4H, m, Ar*H*), 7.45–7.35 (6H, m, Ar*H*), 4.26 (1H, q, *J*=6.8, C*H*OTBS), 3.89 (1H, dd, *J*=9.2, *J*=2.4, C*H*OH), 3.81 (1H, dd, *J*=9.6, *J*=4.8, $CH_xH_yOTBDPS$), 3.74 (1H, dd, *J*=9.6, *J*=4.8, $CH_xH_yOTBDPS$), 3.27 (1H, qd, *J*=7.2, *J*=2.4, $COCHCHOH$), 1.82–1.72 (1H, m, $CHCH_2OTBDPS$), 1.33 (3H, d, *J*=6.8, $CH_3CHOTBS$), 1.13 (3H, d, *J*=7.2, $COCH(CH_3)CHOH$), 1.05 (9H, s, $SiC(CH_3)_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.91 (3H, d, *J*=6.8, $CH(CH_3)CH_2OTBDPS$), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$); $^{13}C$ NMR ($CDCl_3$, 100.6 MHz) $\delta$ 218.4 (C), 135.6 (CH), 133.5 (C), 133.4 (C), 129.6 (CH), 127.6 (CH), 74.4 (CH), 72.6 (CH), 66.9 ($CH_2$), 41.8 (CH), 37.7 (CH), 26.9 ($CH_3$), 25.7 ($CH_3$), 21.3 ($CH_3$), 19.3 (C), 18.0 (C), 13.6 (CH), 9.1 (CH), −4.6 ($CH_3$), −4.9 ($CH_3$); HRMS (+ESI): calcd for $[M+Na]^+$ $C_{31}H_{50}O_4Si_2Na$: 565.3140; found: 565.3159.

**4.6.2. (2*S*,4*R*,5*R*,6*S*)-2-*tert*-Butyldimethylsilyloxy-6-*tert*-butyldiphenylsilyloxy-5-hydroxy-4-methyl-3-heptanone (18).** Yellowish oil; $R_f$=0.15 (hexanes/EtOAc 96:4); $[\alpha]_D$ +9.9 (*c* 1.2, $CHCl_3$); IR (film): $\nu$ 3500 (br), 1710; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.75–7.60 (4H, m, Ar*H*), 7.45–7.35 (6H, m, Ar*H*), 4.19 (1H, q, *J*=6.7, C*H*OTBS), 3.83 (1H, dd, *J*=6.4, *J*=4.7, C*H*OH), 3.81–3.76 (1H, m, C*H*OTBDPS), 3.41 (1H, qd, *J*=7.0, *J*=4.7, $COCHCHOH$), 1.32 (3H, d, *J*=6.7, $CH_3CHOTBS$), 1.09 (3H, d, *J*=7.0, $COCH(CH_3)CHOH$), 1.06 (9H, s, $SiC(CH_3)_3$), 1.02 (3H, d, *J*=6.0, $CH(OTBDPS)CH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 217.3 (C), 135.9 (CH), 135.8 (CH), 134.3 (C), 133.2 (C), 129.8 (CH), 129.6 (CH), 127.7 (CH), 127.4 (CH), 75.1 (CH), 74.5 (CH), 69.7 (CH), 41.4 (CH), 27.1 ($CH_3$), 25.8 ($CH_3$), 21.3 ($CH_3$), 19.2 (C), 19.1 ($CH_3$), 18.1 (C), 11.7 ($CH_3$), −4.7 ($CH_3$), −4.8 ($CH_3$); HRMS (+FAB): calcd for $[M+Na]^+$ $C_{30}H_{48}O_4Si_2Na$: 551.2989; found: 551.2979.

### 4.7. Synthesis of hemiacetal 20 from 16

A 0.025 M solution of TBAF·$3H_2O$ and AcOH in DMF (4.3 mL, 108 μmol) was added to a 10 mL round bottom flask containing **16** (117 mg, 215 μmol) and the resulting mixture was stirred for 3.5 h at rt. Then, it was diluted with $Et_2O$ (30 mL) and $H_2O$ (30 mL), and the organic layer was washed with brine (25 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (from hexanes to hexanes/EtOAc 85:15), which afforded 17 mg (56 μmol, 52% yield) of oil. Spectroscopic analysis of this oil revealed that the main component (9:1 mixture) was cyclic hemiacetal **20**. Colorless oil; $R_f$=0.15 (hexanes/EtOAc 85:15); IR (film): $\nu$ 3510 (br), 2931, 1115, 1038, 1014; $^1H$ NMR ($C_6D_6$, 400 MHz) $\delta$ 3.92 (1H, d, *J*=10.9, CHO*H*), 3.65 (1H, t, *J*=11.8, $CH_xH_yO$), 3.58 (1H, q, *J*=6.3, C*H*OTBS), 3.51 (1H, s, O*H*), 3.48–3.39 (1H, m, C*H*OH), 3.21 (1H, dd, *J*=11.8, *J*=5.5, $CH_xH_yO$), 1.92 (1H, qd, *J*=7.2, *J*=2.7, $O_2CCHCH_3$), 1.79–1.67 (1H, m,

C*H*$CH_2O$), 0.96 (3H, d, $J$=6.3, C$H_3$CHOTBS), 0.93 (9H, s, SiC($CH_3$)$_3$), 0.88 (3H, d, $J$=6.8, CHC$H_3$$CH_2O$), 0.63 (3H, d, $J$=7.2, $O_2$CCHC$H_3$), 0.07 (3H, s, SiC$H_3$), 0.05 (3H, s, SiC$H_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.94–3.90 (1H, m, CHO*H*), 3.71 (1H, t, $J$=11.8, C$H_x$H$_y$O), 3.70 (1H, s, O*H*), 3.66 (1H, q, $J$=6.3, C*H*OTBS), 3.52–3.45 (1H, m, C*H*OH), 3.41 (1H, dd, $J$=11.8, $J$=5.4, C$H_x$$H_y$O), 2.10–1.90 (2H, m, 2×C*H*$CH_3$), 1.10 (3H, d, $J$=6.3, C$H_3$CHOTBS), 0.94 (3H, d, $J$=7.1, CHC$H_3$), 0.88 (9H, s, SiC($CH_3$)$_3$), 0.88 (3H, d, $J$=6.8, CHC$H_3$), 0.07 (3H, s, SiC$H_3$), 0.05 (3H, s, SiC$H_3$); $^{13}$C NMR ($CDCl_3$, 100.6 MHz) $\delta$ 99.0, 75.0, 71.1, 61.4, 37.9, 29.1, 25.8, 18.2, 17.4, 12.8, 12.7, −4.6, −5.1.

### 4.8. Synthesis of lactone 22 from 18

A mixture of **18** (201 mg, 0.38 mmol) and 48% aq HF (45 μL, 1.25 mmol) in $CH_3CN$ (4.5 mL) was stirred at rt under $N_2$ for 45 min. Then, it was diluted with $CH_2Cl_2$ (100 mL), washed with satd $NaHCO_3$ (2×50 mL), dried ($Na_2SO_4$), and concentrated. The purification of the residue by flash chromatography (hexanes/EtOAc 4:1) afforded 133 mg (0.32 mmol, 84%) of (2*S*,4*R*,5*R*,6*S*)-6-*tert*-butyldiphenylsilyloxy-2,5-dihydroxy-4-methyl-3-pentanone (**21**). Next, a mixture of **21** (127 mg, 306 μmol) and $NaIO_4$ (635 mg, 3 mmol) in MeOH/$H_2O$ 2:1 (3.5 mL) was stirred at rt for 1.5 h, diluted with $CH_2Cl_2$ (50 mL), and washed with 0.5 M HCl (2×10 mL). The aqueous layers were extracted with $CH_2Cl_2$ (2×10 mL) and the combined extracts were dried ($Na_2SO_4$) and concentrated, which provided a brownish oil (123 mg) that was used in the next step without further purification. A mixture of this oil and 48% aq HF (110 μL, 3.2 mmol) in $CH_3CN$ (1.5 mL) was stirred at rt under $N_2$ for 60 h. Then, it was diluted with $CH_2Cl_2$ (100 mL), washed with satd $NaHCO_3$ (2×50 mL), dried ($Na_2SO_4$), and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 2:1), which afforded 18 mg (138 μmol, 45% yield over two steps) of (2*R*,3*R*,4*S*)-3-hydroxy-2,4-dimethylbutyrolactone (**22**). Brown solid; mp= 59.0–60.5 °C; $R_f$=0.10 (hexanes/EtOAc 2:1); $[\alpha]_D$ −23.5 (*c* 1.0, $CHCl_3$); IR (KBr): $\nu$ 3463 (br), 1746; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 4.22 (1H, dq, $J$=7.6, $J$=6.1, COOC*H*), 3.76–3.67 (1H, m, C*H*OH), 2.75 (1H, br s, O*H*), 2.60 (1H, dq, $J$=9.2, $J$=7.2, C*H*COO), 1.46 (3H, d, $J$=6.1, COOCHC$H_3$), 1.31 (3H, d, $J$=7.2, OOCCHC$H_3$); $^{13}$C NMR ($CDCl_3$, 75.4 MHz) $\delta$ 176.7, 80.5, 80.0, 43.9, 18.0, 12.5.

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