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Highly stereoselective titanium-mediated aldol reactions from chiral α-silyloxy ketones. A reliable tool for the synthesis of natural products

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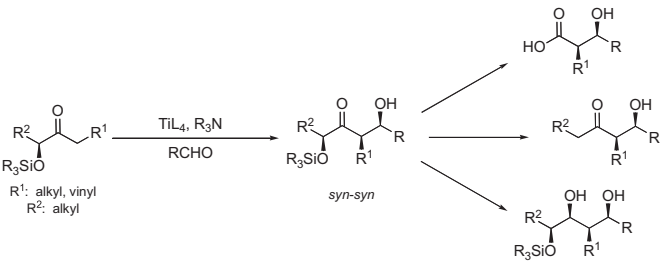
ABSTRACT

Chiral α-silyloxy ketones participate in highly stereoselective $TiCl_4$-mediated aldol reactions that afford diastereomerically pure *syn–syn* adducts in high yield irrespective of the R^1 and R^2 substituents flanking the carbonyl or the silicon protecting group. Further manipulation of the resulting aldol adducts provide in a straightforward manner highly functionalized fragments that facilitate the synthesis of natural products.

1. Introduction

The synthesis of increasingly complex natural products has stimulated the continuous development of synthetic methodologies with greater selectivity and efficiency.[1–3] Particularly, there is a need for selective and high yielding transformations in the coupling of elaborate fragments in advanced steps of a synthetic sequence, where the constraints imposed by the structure of the reaction partners hinder existing methodologies. Stereoselective aldol reactions are a good example of these challenges,[4] in which the concurrent construction of a new carbon–carbon bond and the introduction of one or two new stereocenters often depend on accurate substrate-controlled processes.[5] Therefore, successful application of these reactions requires reliable knowledge of their scope and mechanistic basis in order to predict the outcome of any transformation. In this context, we reported that the titanium-mediated aldol reactions from (*S*) 2-*tert*-butyldimethylsilyloxy-3-pentanone give the corresponding *syn–syn* adducts in a highly stereoselective manner.[6,7] However, the influence of structural elements of other α-silyloxy ketones, such as R^1, R^2 or the protecting silicon group on the stereochemical outcome of related reactions was unclear (Scheme 1).[8,9] Here, we document a comprehensive study of titanium-mediated aldol reactions from chiral α-silyloxy ketones. Our results demonstrate that these transformations provide an appropriate entry to the *syn* arrays embedded in a wide number of natural products.



Scheme 1. Titanium-mediated aldol reactions of chiral α-silyloxy ketones and further transformations.

2. Results and discussion

2.1. Influence of R^1 group

Our previous findings on the enolization of (*S*)-*tert*-butyldimethylsilyloxy-3-pentanone (**1** in Scheme 2) with TiL_4/*i*-Pr_2NEt and the subsequent aldol additions of the resulting titanium enolates to a large set of aldehydes led us to assess the influence of R^1 group on parallel titanium-mediated aldol reactions based on lactate-derived α-*tert*-butyldimethylsilyloxy ketones **2**–**5**. Alkyl ketones **1**–**4** were easily prepared by acylation of the corresponding alkyl lithium reagents with amide **6** (Scheme 2).[10] However, allyl counterparts were too reactive and ketone **5** was obtained in low yields

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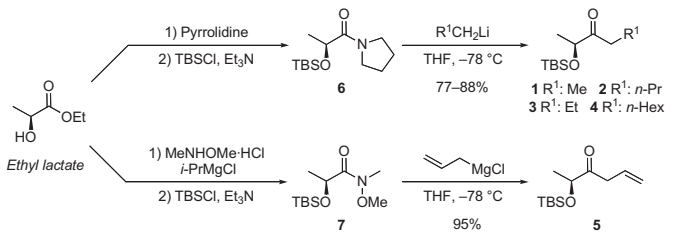
because of the formation of the undesired tertiary alcohol derivative even at −100 °C. Finally, (*S*)-2-*tert*-butyldimethylsilyloxy-5-hexen-3-one (**5**) was prepared by addition of allyl magnesium chloride to Weinreb amide **7**[7] in an excellent yield (Scheme 2).



Scheme 2. Lactate-derived α-*tert*-butyldimethylsilyloxy ketones.

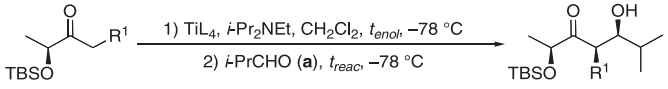
Given that the success of the titanium-mediated aldol reactions from ethyl ketone **1** relies to some extent on the titanium Lewis acid, we first surveyed the enolization of model ketone **2** with several Lewis acids and the addition of the resulting titanium enolate to isobutyraldehyde (**a**). The results are summarized in Table 1.

enolizations even at longer reaction times and gave moderate yields of **9a** (entries 5–7 in Table 1). These results restrict the application of $TiCl_3$(*i*-PrO) to ketone **1**, although it was also successful in the addition of propyl ketone **3**, which holds a small R^1 group (R^1: Me for **1**, R^1: Et for **3**), to chiral aldehyde **b** (Scheme 3). On this occasion, long enolization and reaction times allowed an 85% yield of diastereomerically pure aldol **10b**, an advanced intermediate in the synthesis of **11**, the C1–C17 fragment of salinomycin (Scheme 3, see also Scheme 10).[11]

In spite of this result, $TiCl_4$ appeared to be a more general and reliable titanium Lewis acid and was chosen for the following studies. The optimized conditions were then used for the aldol additions of ketones **2**–**4** to representative aldehydes. The results are summarized in Table 2.

Our findings show that titanium-mediated aldol reactions from lactate-derived α-*tert*-butyldimethylsilyloxy ketones **1**–**4** are highly stereoselective transformations that deliver the corresponding 2,4-*syn*-4,5-*syn* adducts **8**–**10**, and **12** in a simple and efficient manner irrespective of the R^1 group. This methodology has already been used in the key step of the synthesis of NFX-2 and antimycinone (**13** and **14**, respectively, in Scheme 4), where the

Table 1
Titanium-mediated aldol reactions from lactate-derived α-*tert*-butyldimethylsilyloxy ketones



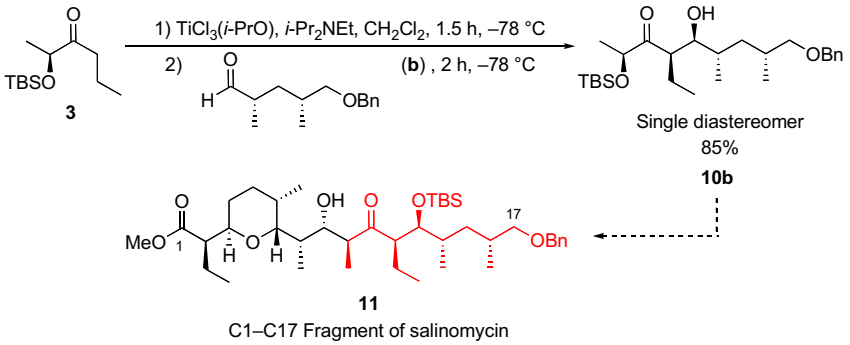
1 R^1: Me
2 R^1: Pr
8a R^1: Me
9a R^1: Pr

Entry	Ketone	Lewis acid	t_{enol} (h)	t_{reac} (h)	Conversion (%)[a]	Aldol	dr[a]	Yield (%)[b]
1	**1**	$TiCl_4$	0.5	0.5	100	**8a**	>97:3	85
2	**1**	$TiCl_3$(*i*-PrO)	0.5	0.5	>95	**8a**	>97:3	85
3	**1**	$TiCl_2$(*i*-PrO)$_2$	1.5	2.0	40	**8a**	>97:3	35
4	**2**	$TiCl_4$	0.5	0.5	100	**9a**	>97:3	81
5	**2**	$TiCl_3$(*i*-PrO)	0.5	0.5	80	**9a**	>97:3	63
6	**2**	$TiCl_3$(*i*-PrO)	0.5	1.5	80	**9a**	>97:3	67
7	**2**	$TiCl_3$(*i*-PrO)	1.5	0.5	90	**9a**	>97:3	75
8	**2**	$TiCl_2$(*i*-PrO)$_2$	1.5	2.0	<30	**9a**	nd	nd

[a] Determined by ^{1}H NMR.
[b] Isolated yield.

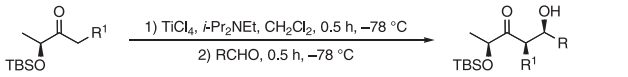
As expected, aldol reactions from ketones **1** and **2** were similar. The enolization of these two ketones with $TiCl_4$ for 30 min and addition of the resulting enolate to 1.5 equiv of isobutyraldehyde for 30 min at −78 °C furnished 2,4-*syn*-4,5-*syn* adducts **8a** and **9a** as a single diastereomer (dr>97:3) in high yields (see entries 1 and 4 Table 1). In turn, mild Lewis acid $TiCl_2$(*i*-PrO)$_2$ proved unsuitable since longer enolization and reaction times did not promote their quantitative enolization (see entries 3 and 8 in Table 1). Ketone **2**, which holds a larger R^1 group than ketone **1** (R^1: Me for **1**, R^1: Pr for **2**), required a strong Lewis acid like $TiCl_4$, because $TiCl_3$(*i*-PrO) provided partial addition of the titanium enolate from ketone **4** to just 1.25 equiv of aldehyde **d** gives a single diastereomer of aldol **12d** in 84% yield (see also Scheme 9).[12]

Having confirmed the success of the aldol methodology with several lactate-derived alkyl ketones, we tackled the reactivity of allyl ketone **5**. We were especially interested in this ketone because it was expected to be more easily enolizable than **1**–**4** and the resulting titanium enolates would contain two reacting positions, α and γ. These offered the possibility of accessing 2,4-*syn*-4,5-*syn* or vinylogous aldol adducts, depending on the predominant reacting position, α or γ, respectively (Scheme 5).[13]



Scheme 3. $TiCl_3$(*i*-PrO)-Mediated aldol reaction of ketone **3**.

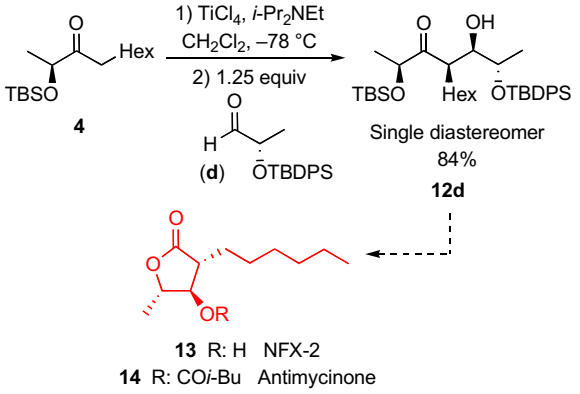
Table 2
$TiCl_4$-Mediated aldol reactions from ketones **2**–**4**



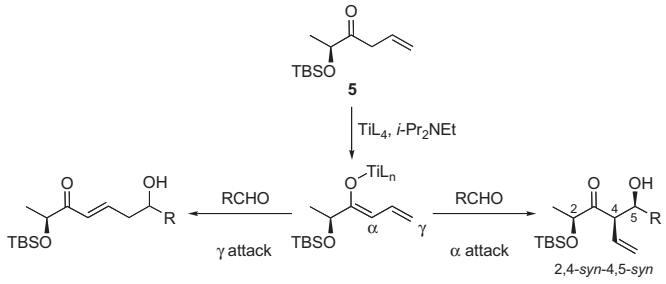
2 R^1: Pr **3** R^1: Et **4** R^1: Hex — **9** R^1: Pr **10** R^1: Et **12** R^1: Hex

Entry	Ketone	R^1	Aldehyde	R	Equiv	Aldol	dr[a]	Yield (%)[b]
1	**2**	Pr	**a**	*i*-Pr	1.5	**9a**	>97:3	81
2	**2**	Pr	**c**	Ph	1.2	**9c**	>97:3	77
3	**3**	Et	**a**	*i*-Pr	1.5	**10a**	>97:3	89
4	**3**	Et	**c**	Ph	1.2	**10c**	>97:3	75
5	**4**	Hex	**a**	*i*-Pr	1.5	**12a**	>97:3	87

[a] Determined by ^{1}H NMR.
[b] Isolated yield.



Scheme 4. Aldol step from ketone **4** towards NFX-2 and antimycinone.

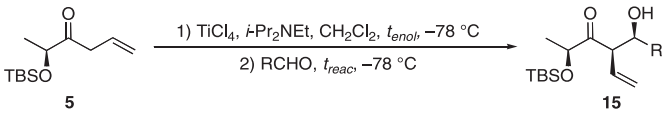


Scheme 5. Alternative aldol reactions of titanium enolate from ketone **5**.

Keeping in mind this possibility, the reaction mixtures were carefully monitored. However, we did not observe the formation of the vinylogous adducts and the titanium-mediated aldol reaction from lactate-derived allyl ketone **5** consistently proceeded through the α position. Moreover, the higher acidity of ketone **5** was not sufficient and $TiCl_4$ or $TiCl_3$(*i*-PrO) were once again the most appropriate Lewis acids. The results are summarized in Table 3.

As for simple alkyl ketones **1** and **2**, $TiCl_2$(*i*-PrO)$_2$ was too mild to adequately enolize the more acidic ketone **5** and longer enolization and reaction times produced 2,4-*syn*-4,5-*syn* aldol **15a** only in low yield (compare entries 1–3 in Table 3). In turn, $TiCl_4$ and $TiCl_3$(*i*-PrO) gave similar results and furnished **15a** as a single diastereomer in acceptable yields (see entries 1 and 2 in Table 3). The application of the $TiCl_4$-procedure to other aliphatic aldehydes afforded a single diastereomer in acceptable to high yields (entries 4 and 5 in Table 3), but parallel additions to benzaldehyde and crotonaldehyde were troublesome (entries 6 and 7 in Table 3). Analysis of the reaction mixture from benzaldehyde showed that the corresponding aldol **15c** was obtained as a single diastereomer in ca. 80% yield (entry 6 in Table 3); however, our attempts to purify the reaction mixture by column chromatography were unsuccessful and α,β-unsaturated ketone **16** was obtained instead (Scheme 6). In turn, the expected aldol adduct **15g** from crotonaldehyde was not observed in the reaction mixtures and conjugated ketone **16** was also isolated as the only product (entry 7 in Table 3). These results suggest that aldol adducts **15c** and **15g** are thermodynamically unstable and that they decompose to deliver the α,β-unsaturated ketone **16**, which should be considered for further applications of related methodologies.

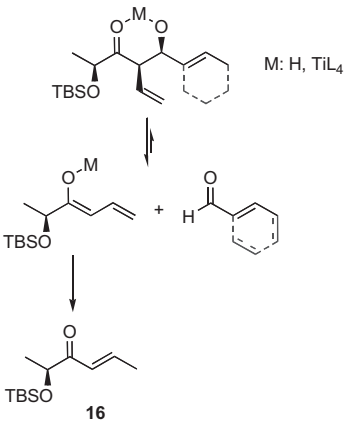
Table 3
Titanium-mediated aldol reactions from allyl ketone **5**



5 — **15**

Entry	Lewis acid	t_{enol} (h)	t_{reac}(h)	Aldehyde	R	Equiv	Aldol	dr[a]	Yield (%)[b]
1	$TiCl_4$	0.5	0.5	**a**	*i*-Pr	1.5	**15a**	>97:3	74
2	$TiCl_3$(*i*-PrO)	0.5	0.5	**a**	*i*-Pr	1.5	**15a**	>97:3	75
3	$TiCl_2$(*i*-PrO)$_2$	1.5	2.0	**a**	*i*-Pr	1.5	**15a**	>97:3	35
4	$TiCl_4$	0.5	0.5	**e**	*i*-Bu	1.5	**15e**	>97:3	80
5	$TiCl_4$	0.5	0.5	**f**	Et	1.5	**15f**	>97:3	67
6	$TiCl_4$	0.5	0.5	**c**	Ph	1.2	**15c**	>97:3	(80)[c]
7	$TiCl_4$	0.5	0.5	**g**	(*E*) CH=CHCH$_3$	1.2	**15g**	—	—

[a] Determined by ^{1}H NMR.
[b] Isolated yield.
[c] Crude yield.



Scheme 6. Decomposition of conjugated aldol adducts from allyl ketone **5**.

2.2. Influence of R^2 group

Having established the generality of the aldol methodology based on lactate-derived ketones, we examined the effect of R^2 group. For this purpose and in order to expand the scope of this reaction to any α-silyloxy ketone, we studied the aldol reactions of α-*tert*-butyldimethylsilyloxy ethyl ketones **17** and **18**, which hold R^2 groups of diverse steric hindrance (R^2: Bn and *i*-Pr, respectively, see Fig. 1).[14]

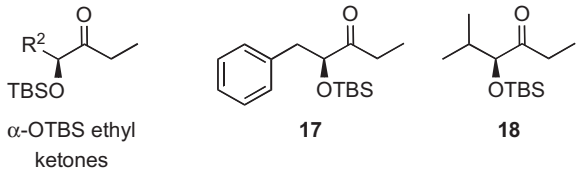


Fig. 1. Chiral α-*tert*-butyldimethylsilyloxy ethyl ketones.

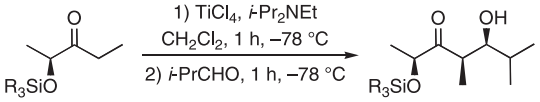
The closeness of bulky R^2 groups to the carbonyl led us to test carefully the experimental conditions of the $TiCl_4$-mediated aldol reactions from these ketones with model aldehydes, such as isobutyraldehyde (**a**) and benzaldehyde (**c**). The results are summarized in Table 4.

Our results reveal that the experimental conditions optimized for lactate-derived ethyl ketone **1** can be safely exported to ketone **17**, thereby allowing diastereoselectively aldol adducts **19** in yields up to 87% (see entries 1 and 3 in Table 4). Indeed, no starting ketone **17** was observed in the crude reaction mixtures and longer reaction times did not improve the yield (compare entries 1 and 2 in Table 4). These observations confirm the efficient enolization provided by $TiCl_4$/*i*-Pr_2NEt and the high reactivity of the ensuing titanium enolate. In contrast, parallel reactions from ketone **18** containing an R^2-isopropyl group were more sluggish. Short reaction times produced the expected aldol adducts **20** in a highly stereoselective way but in moderate yields, since relatively large amounts of the starting ketone **18** were isolated for isobutyraldehyde as well as benzaldehyde (30% and 20%, respectively, see entries 4 and 6 in Table 4). These figures were improved by extending reaction times (compare entries 4–7 in Table 4). This finding proved that titanium-mediated aldol reactions from α-*tert*-butyldimethylsilyloxy ketones are as sensitive to the steric hindrance of R^2 group as they are to the R^1 group.

2.3. Influence of the silicon protecting group

Finally, we studied the effect of the silicon group on the stereochemical outcome of these reactions. Although the *tert*-butyldimethylsilyl-protecting group (TBS) used up to this point is probably the most common protecting group of alcohols, we tested the stability and influence of other silicon groups on these titanium-mediated aldol reactions. We were particularly aware of the labile triethylsilyl group (TES), which is often used in the synthesis of natural products. Therefore, lactate-derived ethyl ketones **21**–**23** possessing sensitive and robust silicon protecting groups, from TES to TIPS, were submitted to the same enolization conditions and the resulting titanium enolates underwent aldol additions to 1.5 equiv of isobutyraldehyde (**a**) for 1 h. The results are summarized in Table 5.

Table 5
$TiCl_4$-Mediated aldol reactions of ethyl α-silyloxy ketones **21**–**23**



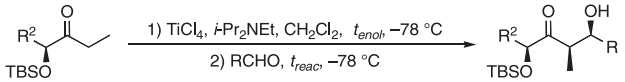
21 R_3Si: TES
22 R_3Si: TBDPS
23 R_3Si: TIPS

24a R_3Si: TES
25a R_3Si: TBDPS
26a R_3Si: TIPS

Entry	Ketone	R_3Si	Aldol	dr[a]	Yield (%)[b]
1	**21**	TES	**24a**	>97:3	82
2	**22**	TBDPS	**25a**	>97:3	79
3	**23**	TIPS	**26a**	>97:3	80

[a] Determined by ^1H NMR.
[b] Isolated yield.

Table 4
Titanium-mediated aldol reactions from ethyl ketones **17** and **18**



17 R^2: Bn **18** R^2: *i*-Pr

19 R^2: Bn **20** R^2: *i*-Pr

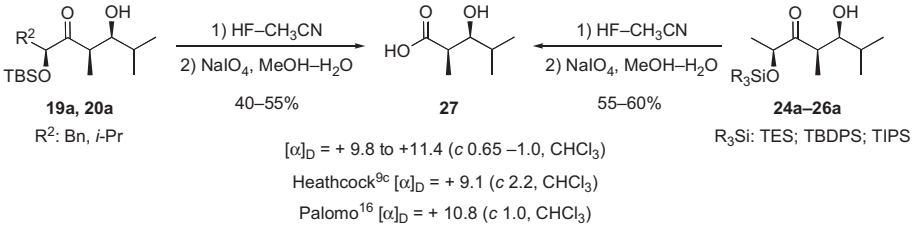
Entry	Ketone	t_{enol} (h)	t_{reac} (h)	Aldehyde	R	Equiv	Aldol	dr[a]	Yield (%)[b,c]
1	**17**	0.5	0.5	**a**	*i*-Pr	1.5	**19a**	>97:3	87
2	**17**	1.5	2.0	**a**	*i*-Pr	1.5	**19a**	>97:3	86
3	**17**	0.5	0.5	**c**	Ph	1.2	**19c**	>97:3	82
4	**18**	0.5	0.5	**a**	*i*-Pr	1.5	**20a**	>97:3	52 (30)
5	**18**	1.5	1.0	**a**	*i*-Pr	1.5	**20a**	>97:3	70
6	**18**	0.5	0.5	**c**	Ph	1.2	**20c**	>97:3	64 (20)
7	**18**	1.5	1.0	**c**	Ph	1.2	**20c**	>97:3	75

[a] Determined by ^1H NMR.
[b] Isolated yield.
[c] Into parentheses, recovered ketone **18**.

The silicon protecting groups had no effect on the titanium-mediated aldol additions from α-silyloxy ketones. The diastereoselectivity and the yield of these transformations and those described for α-OTBS ketone **1** were similar (compare entry 1 in Table 1 and entries 1–3 in Table 5). Even the sensitive TES group was stable under the reaction conditions and the corresponding adduct **24a** was isolated in high yield (entry 1 in Table 5). These observations indicate that the transformations are highly flexible, and so they are suitable for advanced steps of a synthetic sequence.

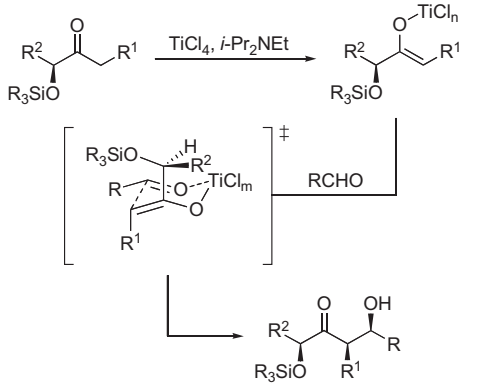
2.4. Stereochemistry and mechanism

The absolute configuration of aldol products **8** resulting from ethyl ketone **1** was firmly established through chemical correlation, NMR and X-ray diffraction studies.[7,15] Taking advantage of these results, the stereochemistry of aldol adducts **9**, **10**, **12** and **15** from lactate-derived ketones **2**–**5** was initially assigned as 2,4-*syn*-4,5-*syn* and was later confirmed during the application to the synthesis of natural products. In turn, the absolute configuration of aldol adducts from ketones containing bulky R^2 groups, **19a**–**20a**, or different silicon protecting groups, **24a**–**26a**, was confirmed by chemical correlation. Thus, removal of the protecting groups and subsequent oxidation of the resulting dihydroxy ketones furnished β-hydroxy carboxylic acid **27**, whose spectroscopic data matched those reported in the literature for (2*R*,3*S*) 3-hydroxy-2,4-dimethylpentanoic acid (Scheme 7).[9c,16]



Scheme 7. Chemical correlation to (2*R*,3*S*) 3-hydroxy-2,4-dimethylpentanoic acid.

This information and the stereochemical outcome of the reactions reported so far support a common mechanistic picture for these transformations in which the enolization of an α-silyloxy ketone produces a *Z*-enolate that evolves through a cyclic six-membered transition state. Remarkably, no vinylogous aldol adducts were observed from allyl ketone **5**, thereby ruling out alternative open transition states. In such a scenario, the antiperiplanar distribution of R_3SiO–C and C–OTi bonds would be the key element determining the stereochemical outcome of the reaction since the preferred chair transition state places the less sterically demanding substituent (H vs Me, Bn, or *i*-Pr) of the Cα stereocenter pointing towards the inside of the ring (Scheme 8), as previously proposed for related systems.[9c,17,18]



Scheme 8. Mechanism for the titanium-mediated aldol reactions based on α-silyloxy ketones.

2.5. Synthetic applications

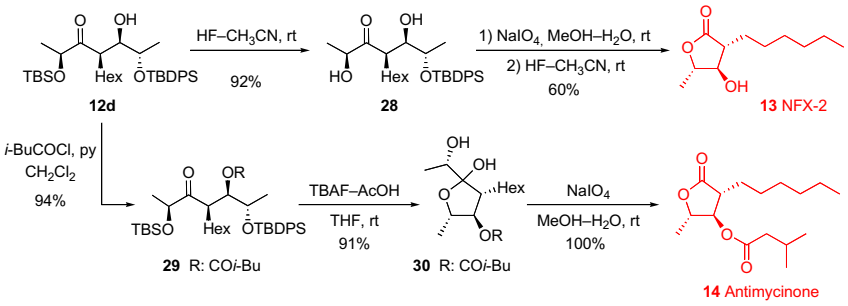
Having demonstrated that the titanium-mediate aldol reactions based on chiral α-silyloxy ketones occur in a highly stereoselective manner irrespective of the R^1, R^2 and silicon protecting groups, we next explored the conversion of the ensuing adducts into arrays embedded in the structure of natural products. Our first target dealt with the removal of the original Cα stereocenter.

Masamune proved that removal of the hydroxyl protecting group of this sort of aldol adducts followed by the oxidation of the resulting α-hydroxy ketone delivers enantiomerically pure β-hydroxy carboxylic acids in good yields.[9a] This synthetic sequence was used to confirm the configuration of the aldol adducts shown in Scheme 7. Moreover, it was successfully applied to the synthesis of NFX-2 and antimycinone (Scheme 9).[19,20] Treatment of aldol **12d** (see Scheme 4) with HF in CH_3CN led to α-hydroxy ketone **28**, which was oxidized and deprotected to afford NFX-2 (**13** in Scheme 9) in 60% yield. Alternatively, acylation of **12d** and simultaneous TBS and TBDPS deprotection of the resulting keto ester **29** furnished a mixture of hemiketals **30**, which was smoothly oxidized with $NaIO_4$ to produce antimycinone (**14** in Scheme 9) in quantitative yield. Thus, these synthetic sequences from chiral ketone **4** furnish enantiomerically pure metabolites **13** and **14** in four steps and 46% and 71% yield, respectively, from α-OTBS ketone **4**,[21] which prove the high efficiency of the titanium-mediated aldol reaction based on α-silyloxy ketones.

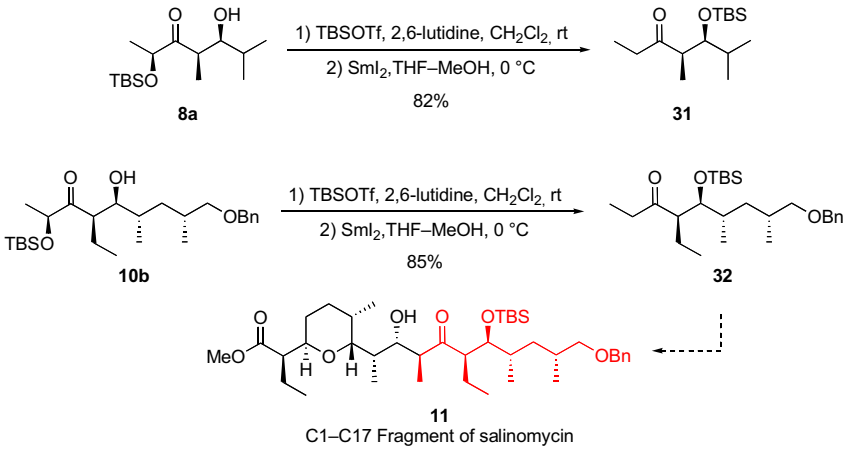
The selective removal of the α-$OSiR_3$ functionality without affecting the carbon skeleton was our next objective. Preliminary experiments with SmI_2 proved that it was impossible to carry out this reduction on unprotected aldol adducts. In contrast, TBS-protection of the β-hydroxyl group of **8a** followed by treatment of the resulting aldol with SmI_2 nicely furnished ethyl ketone **31** in 82% yield (Scheme 10).[22,23] This sequence was applied to aldol **10b** (see Scheme 3) for the preparation of ketone **32**, an advanced intermediate for the synthesis of the C1–C17 fragment of salinomycin **11** (Scheme 10).[11]

We also addressed the stereoselective reduction of the carbonyl bond to obtain enantiomerically pure 1,2,4-triols. Taking advantage of well established stereoselective reductions of β-hydroxy ketones,[24] we first assessed the *anti* reduction of the C=O bond of model aldol adducts **8a** and **8h**[25] (R: *i*-Pr, $C(CH_3)C{=}CH_2$, respectively, Scheme 11). In spite of our attempts, neither the classical Evans–Chapman–Carreira[26] reduction nor other substrate-controlled methodologies succeeded,[27] affording mixtures of *anti* and *syn* diols **33** and **34** in a poor diastereomeric ratio.

The low stereocontrol observed for these reductions can be traced to the protected hydroxyl group at the α-position to the carbonyl. The rationale for the expected *anti* stereochemistry of this reduction assumes that the internal hydride delivery proceeds through a six-membered transition state in which the activated carbonyl group is placed at an axial position (**I** in Scheme 11). However, the antiperiplanar arrangement of the electron-withdrawing OTBS group relative to the C=O bond forces the hydride to follow the less favoured trajectory according to the



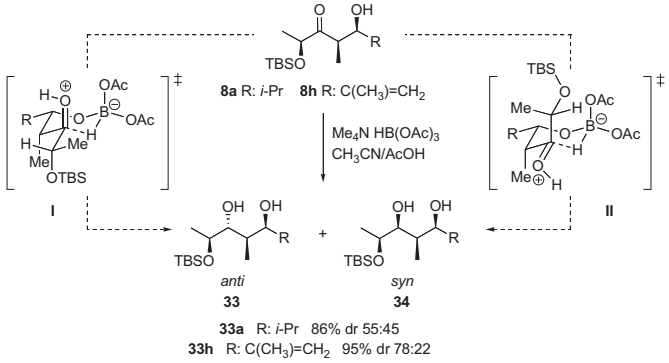
Scheme 9. Synthesis of NFX-2 and antimycinone from aldol **12d**.



Scheme 10. Removal of the α-OTBS group by reduction with SmI_2.

Cornforth model.[28,29] Thus, alternative transition state **II** (Scheme 11) can contribute to the reaction and the sterically favoured transition state **I** cannot override the electronically favoured **II**, which may explain the dramatic loss of stereocontrol observed in the reduction of aldol products **8a** and **8h**.

In contrast, parallel reductions directed towards *syn*-diols proceeded with excellent diastereoselectivity. Thus, the Narasaka–Prasad[30] procedure delivered diols **34** as a single diastereomer in high yields. As shown in Scheme 12, this methodology was used for the stereoselective reduction of *ent*-**8h**[25] leading to diol *ent*-**34h** as a single diastereomer (dr>97:3) in an excellent 94% yield. Treatment of *ent*-**34h** with BH_3 followed by oxidative work-up furnished a 4:1 mixture of diastereomers, which was purified to deliver all-*syn* triol **35** in 60% yield. Selective protection of primary alcohol with pivaloyl chloride and the resulting diol with $Me_2C(OMe)_2$ afforded acetonide **36** in 61% yield

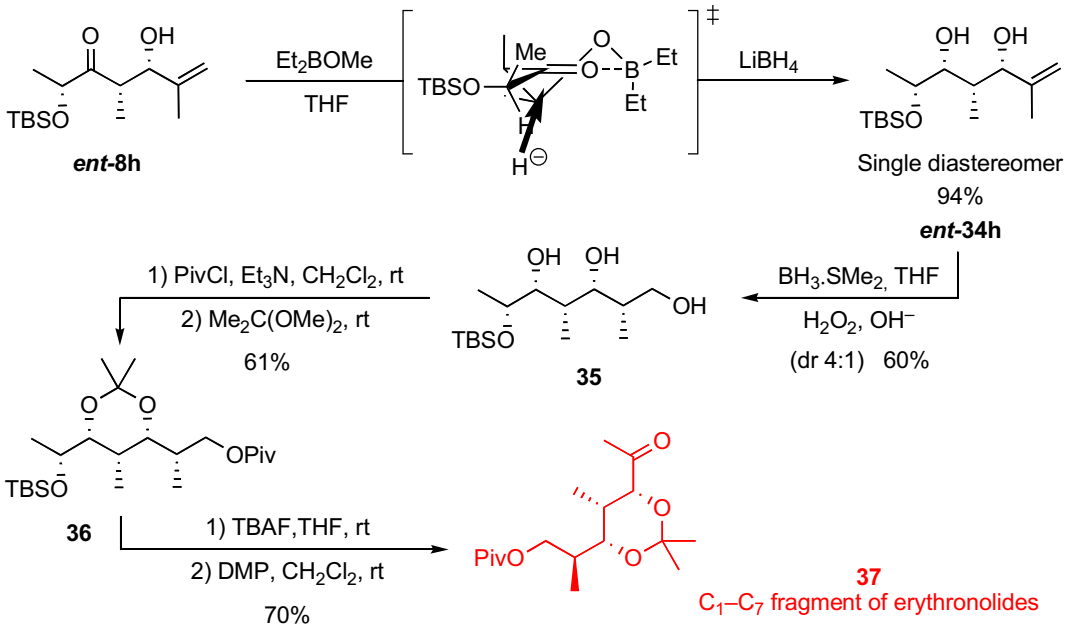


Scheme 11. Substrate-controlled synthesis of *anti*-diols from aldol adducts.

over two steps. Finally, removal of the silicon protecting group at C6 and Dess–Martin oxidation[31] of the ensuing alcohol afforded the C1–C7 fragment of erythronolides **37** in 70% yield.[32] Once again, the Cα stereocenter in the starting α-silyloxy ketone *ent*-**1** becomes the key element to install all the stereocenters to finally afford the desired fragment in a straightforward and efficient manner.

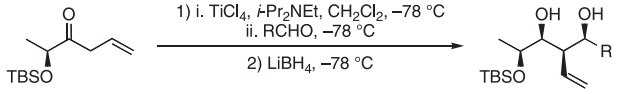
Given that the highly stereoselective reduction of 2,4-*syn*-4,5-*syn* aldol *ent*-**8h** to *syn*-diol *ent*-**34** presumably proceeded through the chelated boron aldolate shown in Scheme 12, we envisaged that a sequential transformation based on a titanium-mediated aldol reaction from ketone **1** followed by reduction of the resultant titanium aldolate with $LiBH_4$ might also occur. This approach was right and provided straightforward access to the desired *syn*-diols **34** in a one-pot transformation.[15] In view of this successful transformation, we studied a similar procedure from allyl ketone **5** that would supply highly functionalized *syn*-diols **38**. The results are summarized in Table 6.

The stereochemical outcome of these reactions confirm the synthetic potential of the sequential aldol-reduction transformations based on chiral α-silyloxy ketones. As for ketones **1**, diastereomerically pure *syn*-diols **38** were obtained in good to high yields in a straightforward manner.[33] Remarkably, diol **38c** derived from benzaldehyde was isolated in 80% yield. This observation implies that the titanium aldolate shows enough stability to be trapped by the reducing agent. In contrast, diol **38g** from crotonaldehyde was not observed in the reaction mixtures. The absence of the reduced product demonstrates that the aldol of allyl ketone **5** and crotonaldehyde is not produced as expected. With this exception, the reduction of the C=O bond of titanium aldolates from α-silyloxy ketones furnished the corresponding *syn*-diols in a highly stereoselective manner.



Scheme 12. Substrate-controlled synthesis of *syn*-diols from aldol adducts.

Table 6
Sequential $TiCl_4$-mediated aldol reaction and $LiBH_4$ reduction from allyl ketone **5**



Entry	Aldehyde	R	Equiv	Diol	dr[a]	Yield (%)[b]
1	**a**	*i*-Pr	1.5	**38a**	>97:3	72
2	**e**	*i*-Bu	1.5	**38e**	>97:3	66
3	**i**	$(CH_2)_{12}CH_3$	1.5	**38i**	>97:3	83
4	**c**	Ph	1.2	**38c**	>97:3	80
5	**g**	(*E*) CH=CHCH$_3$	1.2	**38g**	—	—

[a] Determined by ^{1}H NMR.
[b] Isolated yield.

3. Conclusions

In summary, titanium enolates from a broad scope of chiral α-silyloxy ketones participate in highly stereoselective aldol reactions. Our systematic study of the influence of a range of structural and experimental variables on the stereochemical outcome of these substrate-controlled reactions has established that the corresponding *syn*–*syn* adducts can be obtained as a single diastereomer in high yield irrespective of the R^1 and R^2 substituents flanking the carbonyl or the silicon protecting group. In turn, these adducts can be converted into highly functionalized fragments in a straightforward manner. A remarkable example is the lactate-derived α-silyloxy allyl ketone, which undergoes highly efficient sequential transformations that lead to high yields of enantiomerically pure *syn* diols containing three new stereocenters. Hence, the titanium-mediated aldol reactions from chiral α-silyloxy ketones are a reliable and powerful tool for the synthesis of natural products.

4. Experimental

4.1. General information

Melting points were taken on an Electrothermal apparatus and are uncorrected. Specific rotations were determined at 20 °C on a Perkin–Elmer 241 MC polarimeter. IR spectra were recorded on a Nicolet 510FT spectrometer and only the more representative frequencies are reported. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian Unity Plus spectrometer; ^{1}H NMR (400 MHz) spectra were recorded on a Varian Mercury; ^{1}H NMR (500 MHz) spectra were recorded on a Varian-500 VXR; chemical shifts (δ) are quoted in parts per million and referenced to internal TMS for ^{1}H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR; where appropriate, 2D techniques were also used to assist in structural elucidation. Mass spectra were obtained from the Centro de Apoio Científico e Tecnoloxico a Investigación (CACTI), Universidade de Vigo and from the Servei d'Espectrometria de Masses, Universitat de Barcelona. 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 and *i*-Pr_2NEt. All other reagents were used as received.

4.2. (*S*)-2-*tert*-Butyldimethylsilyloxy-5-hexen-3-ona (5)

A 1.7 M C_3H_5MgCl in THF (3.5 mL, 6 mmol) was carefully added to a solution of **7** (1.58 g, 6 mmol) in dry THF (90 mL) under N_2 at −78 °C. The resulting mixture was stirred for 15 min at −78 °C and quenched by addition of sat NH_4Cl. It was partitioned with Et_2O and H_2O, the organic layer was washed with brine, dried and concentrated to afford an oil, which was purified by flash chromatography (95:5 hexanes/EtOAc) to give 1.30 g (5.7 mmol, 95% yield) of ketone **5** as a colourless oil; R_f (95:5 hexanes/EtOAc) 0.40; $[\alpha]_D^{20}$ −1.2 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film) 3082, 2956, 2931, 2859, 1731, 1644, 1472, 1254, 1118 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.94 (1H, ddt, *J* 17.2, 10.3, 6.9 Hz, C*H*=CH$_2$), 5.20–5.09 (2H, m, CH=C*H*$_2$), 4.18 (1H, q, *J* 6.9 Hz, C*H*OSi), 3.42 (1H, ddt, *J* 17.9, 6.9, 1.3 Hz, COC*H*$_x$H$_y$), 3.33 (1H, ddt, *J* 17.9, 6.9, 1.3 Hz, COCH$_x$*H*$_y$), 1.29 (3H, d, *J* 6.9 Hz, *Me*CHOSi), 0.92 (9H, s, SiC*Me*$_3$), 0.09 (6H, s, 2× Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 211.9, 130.7, 118.5, 74.7, 41.7, 25.7, 20.9, 18.0, −4.8, −5.1; HRMS (ESI): $[MH]^+$, found 229.1612, $C_{12}H_{25}O_2Si$ requires 229.1618.

4.3. General $TiCl_4$-aldol procedure for α-silyloxy ketones

Neat $TiCl_4$ (0.12 mL, 1.1 mmol) is added slowly to a solution of an α-silyloxy ketone (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_2NEt (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 or 1.2 equiv), stirring is continued for 30 min at −78 °C. The reaction is quenched by the addition of sat NH_4Cl (5 mL) and vigorously stirred at room temperature. The mixture is diluted with Et_2O, washed with H_2O, sat $NaHCO_3$ and brine. The aqueous layers are extracted with Et_2O, and the combined organic extracts are dried ($MgSO_4$) and concentrated. The resulting oil is analyzed by ^1H NMR and purified by flash chromatography (hexanes/EtOAc or CH_2Cl_2).

*4.3.1. (2S,4R,5S)-2-tert-Butyldimethylsilyloxy-5-hydroxy-6-methyl-4-propyl-3-heptanone (**9a**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.25; $[\alpha]_D^{20}$ −22.2 (*c* 1.3, $CHCl_3$); ν_{max} (liquid film) 3524 (br), 2958, 2932, 2859, 1701, 1470, 1256, 1115 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.23 (1H, q, *J* 6.8 Hz, C*H*OSi), 3.45–3.39 (1H, m, COC*H*CHOH), 3.36 (1H, dd, *J* 8.4, 2.7 Hz, C*H*OH), 1.80–1.65 (2H, m, C*H*Me_2 and C$H_xH_y$$CH_2$Me), 1.55–1.43 (1H, m, C$H_xH_y$$CH_2$Me), 1.35–1.15 (2H, m, CH_2CH_2Me), 1.32 (3H, d, *J* 6.8 Hz, *Me*CHOSi), 1.01 (3H, d, *J* 6.4 Hz, CH*Me*), 0.93 (9H, s, SiCMe_3), 0.90 (3H, t, *J* 7.2 Hz, CH_2*Me*), 0.89 (3H, d, *J* 6.8 Hz, CH*Me*), 0.10 (6H, s, 2× Si*Me*); δ_C (100.6 MHz, $CDCl_3$) 218.6, 76.2, 74.9, 46.7, 31.2, 27.2, 25.8, 21.3, 20.5, 19.4, 19.1, 18.1, 14.4, −4.6, −4.7; HRMS (ESI): $[MNa]^+$, found 339.2326, $C_{17}H_{36}NaO_3Si$ requires 339.2325.

*4.3.2. (1R,2R,4S)-4-tert-Butyldimethylsilyloxy-1-hydroxy-1-phenyl-2-propyl-3-pentanone (**9c**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.20; $[\alpha]_D^{20}$ −15.0 (*c* 0.9, $CHCl_3$); ν_{max} (liquid film) 3488 (br), 2957, 2931, 2858, 1709, 1455, 1254, 1117 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.30 (5H, m, Ar*H*), 4.95 (1H, d, *J* 4.5 Hz, C*H*OH), 4.02 (1H, q, *J* 6.9 Hz, C*H*OSi), 3.53–3.46 (1H, m, COC*H*CHOH), 1.78–1.64 (1H, m, C$H_xH_y$$CH_2$Me), 1.57–1.40 (3H, m, C$H_xH_y$$CH_2$Me), 1.23 (3H, d, *J* 6.9 Hz, *Me*CHOSi), 0.93 (9H, s, SiCMe_3), 0.80 (3H, t, *J* 7.3 Hz, CH_2*Me*), 0.09 (3H, s, Si*Me*), 0.08 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 217.2, 142.0, 128.2, 127.4, 126.1, 75.0, 73.2, 52.3, 28.7, 25.8, 20.9, 20.1, 18.1, 14.3, −4.6, −4.7; HRMS (ESI): $[MNa]^+$, found 373.2172, $C_{20}H_{34}NaO_3Si$ requires 373.2169.

*4.3.3. (2S,4R,5S)-2-tert-Butyldimethylsilyloxy-4-ethyl-5-hydroxy-6-methyl-3-heptanone (**10a**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.25; $[\alpha]_D^{20}$ −19.9 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3521 (br), 2960, 2932, 2859, 1705, 1472, 1464, 1256, 1117 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.22 (1H, q, *J* 6.8 Hz, C*H*OSi), 3.41–3.30 (2H, m, C*H*OH and COC*H*-CHOH), 1.85–1.55 (3H, m, C*H*Me_2 and CH_2Me), 1.32 (3H, d, *J* 6.8 Hz, *Me*CHOSi), 1.00 (3H, d, *J* 6.6 Hz, CH*Me*), 0.93 (9H, s, SiCMe_3), 0.89 (3H, d, *J* 6.6 Hz, CH*Me*), 0.87 (3H, t, *J* 7.5 Hz, CH_2*Me*), 0.11 (6H, s, 2× Si*Me*); δ_C (100.6 MHz, $CDCl_3$) 218.4, 76.1, 74.9, 48.4, 31.1, 25.8, 20.4, 19.2 (× 2), 18.2, 18.1, 12.4, −4.6, −4.7; HRMS (ESI): $[MNa]^+$, found 325.2174, $C_{16}H_{34}NaO_3Si$ requires 325.2169.

*4.3.4. (1R,2R,4S)-4-tert-Butyldimethylsilyloxy-2-ethyl-1-hydroxy-1-phenyl-3-pentanone (**10c**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.22; $[\alpha]_D^{20}$ −18.4 (*c* 1.05, $CHCl_3$); ν_{max} (liquid film) 3488 (br), 2956, 2931, 2858, 1709, 1462, 1255, 1120 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.26 (5H, m, Ar*H*), 4.96 (1H, dd, *J* 5.1, 2.2 Hz, C*H*OH), 4.00 (1H, q, *J* 6.7 Hz, C*H*OSi), 3.44 (1H, ddd, *J* 9.2, 5.1, 4.0 Hz, COC*H*CHOH), 1.85–1.68 (1H, m, CH_xH_yMe), 1.67–1.50 (1H, m, CH_xH_yMe), 1.22 (3H, d, *J* 6.7 Hz, *Me*CHOSi), 0.93 (9H, s, SiCMe_3), 0.79 (3H, t, *J* 7.5 Hz, CH_2*Me*), 0.08 (3H, s, Si*Me*), 0.07 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 216.8, 142.1, 128.2, 127.4, 126.1, 75.0, 73.1, 53.8, 25.8, 20.0, 19.6, 18.1, 11.9, −4.6, −4.7; HRMS (ESI): $[MNa]^+$, found 359.2004, $C_{19}H_{32}NaO_3Si$ requires 359.2012.

*4.3.5. (2S,4R,5S)-2-tert-Butyldimethylsilyloxy-4-hexyl-5-hydroxy-6-methyl-3-heptanone (**12a**).* Colourless oil. R_f (95:5 hexanes/EtOAc) 0.10; $[\alpha]_D^{20}$ −15.9 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film) 3510 (br), 2960, 2940, 2860, 1710, 1465, 1120 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.23 (1H, q, *J* 6.7 Hz, C*H*OSi), 3.45–3.30 (2H, m, COC*H*CHOH), 1.80–1.65 (2H, m, COCHCH_xH_y and C*H*Me_2), 1.60–1.45 (1H, m, COCHCH_xH_y), 1.32 (3H, d, *J* 6.7 Hz, *Me*CHOSi), 1.30–1.20 (8H, m, $(CH_2)_4$Me), 1.01 (3H, d, *J* 6.7 Hz, CH*Me*), 0.93 (9H, s, SiCMe_3), 0.89 (3H, d, *J* 6.7 Hz, CH*Me*), 0.87 (3H, t, *J* 6.7 Hz, CH_2*Me*), 0.10 (6H, s, 2× Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 218.5, 76.2, 74.9, 46.9, 31.6, 31.2, 29.7, 28.1, 25.8, 25.1, 22.6, 20.5, 19.4, 19.2, 18.1, 14.0, −4.6 (× 2); HRMS (ESI): $[MNa]^+$, found 381.2805, $C_{20}H_{42}NaO_3Si$ requires 381.2801.

*4.3.6. (2S,4R,5S,6S)-2-tert-Butyldimethylsilyloxy-6-tert-butyldiphenylsilyloxy-4-hexyl-5-hydroxy-3-heptanone (**12d**).* Colourless oil. R_f (60:40 hexanes/CH_2Cl_2) 0.15; $[\alpha]_D^{20}$ −7.9 (*c* 2.0, $CHCl_3$); ν_{max} (liquid film) 3510 (br), 3080, 3060, 2960, 2920, 2850, 1710, 1595, 1470, 1250, 1110 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.70–7.60 (4H, m, *ArH*), 7.50–7.30 (6H, m, Ar*H*), 4.07 (1H, q, *J* 7.0 Hz, C*H*OTBS), 3.72–3.68 (1H, m, C*H*OH), 3.67 (1H, quint, *J* 6.0 Hz, C*H*OTBDPS), 3.38–3.34 (1H, m, COC*H*CH_2), 1.64–1.54 (1H, m, COCHCH_xH_y), 1.39–1.31 (1H, m, COCHCH_xH_y), 1.23 (3H, d, *J* 7.0 Hz, *Me*CHOTBS), 1.21–1.04 (8H, m, $(CH_2)_4$Me), 0.99 (9H, s, SiCMe_3), 0.95 (3H, d, *J* 6.0 Hz, TBDPSOCH*Me*), 0.85 (9H, s, SiCMe_3), 0.79 (3H, t, *J* 7.0 Hz, CH_2*Me*), 0.08 (3H, s, Si*Me*), 0.08 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 216.4, 135.9, 135.8, 134.2, 133.2, 129.8, 129.6, 127.7, 127.4, 75.3, 74.6, 70.0, 46.9, 31.6, 29.7, 27.2, 27.1, 26.3, 25.8, 22.6, 20.6, 19.2, 19.1, 18.1, 14.1, −4.6, −4.7; HRMS (ESI): $[MNa]^+$, found 621.3785, $C_{35}H_{58}NaO_4Si_2$ requires 621.3771.

*4.3.7. (2S,4R,5S)-2-tert-Butyldimethylsilyloxy-5-hydroxy-6-methyl-4-vinyl-3-heptanone (**15a**).* Colourless oil. R_f (95:5 hexanes/EtOAc) 0.25; $[\alpha]_D^{20}$ +195.6 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3522 (br), 3081, 2957, 2931, 2859, 1700, 1633, 1472, 1256, 1116, 1085 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.93–5.81 (1H, m, C*H*=CH_2), 5.34–5.28 (1H, m, CH=CH_2), 4.25 (1H, q, *J* 6.9 Hz, C*H*OSi), 4.03 (1H, dd, *J* 9.2, 3.1 Hz, C*H*OH), 3.51 (1H, dd, *J* 8.2, 2.9 Hz, C*H*CH=CH_2), 1.70–1.60 (1H, m, C*H*Me_2), 1.33 (3H, d, *J* 6.9 Hz, *Me*CHOSi), 0.99 (3H, d, *J* 6.6 Hz, CH*Me*), 0.92 (9H, s, SiCMe_3), 0.87 (3H, d, *J* 6.7 Hz, CH*Me*), 0.08 (3H, s, Si*Me*), 0.07 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 215.5, 131.7, 120.9, 76.2, 74.7, 52.3, 30.8, 25.7, 21.9, 18.9, 18.7, 18.1, −4.8, −4.9; HRMS (ESI): $[MNa]^+$, found 323.2013, $C_{16}H_{32}NaO_3Si$ requires 323.2012.

*4.3.8. (2S,4R,5S)-2-tert-Butyldimethylsilyloxy-5-hydroxy-7-methyl-4-vinyl-3-octanone (**15e**).* Colourless oil. R_f (95:5 hexanes/EtOAc) 0.25; $[\alpha]_D^{20}$ +128.9 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film) 3737, 2956, 2931, 2859, 1701, 1635, 1472, 1258, 1115 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.84 (1H, ddd, *J* 17.1, 10.1, 9.5 Hz, C*H*=CH_2), 5.35–5.25 (1H, m, CH=CH_2), 4.24 (1H, q, *J* 6.9 Hz, C*H*OSi), 3.98 (1H, dt, *J* 9.4, 3.8 Hz, C*H*OH), 3.73 (1H, dd, *J* 9.5, 3.8 Hz, C*H*CH=CH_2), 1.87–1.70 (1H, m, C*H*Me_2), 1.44 (1H, ddd, *J* 13.7, 9.3, 5.3 Hz, CH_xH_yCHMe_2), 1.31 (3H, d, *J* 6.9 Hz, *Me*CHOSi), 1.06 (1H, ddd, *J* 13.7, 8.8, 4.0 Hz, CH_xH_yCHMe_2), 0.92 (9H, s, SiCMe_3), 0.92–0.90 (3H, buried d, CH*Me*), 0.90 (3H, d, *J* 6.4 Hz, CH*Me*), 0.08 (3H, s, Si*Me*), 0.07 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 214.8, 132.3, 121.1, 74.7, 69.0, 55.8, 43.4, 25.8, 24.3, 23.4, 21.8, 21.5, 18.1, −4.8, −4.9; HRMS (ESI): $[MNa]^+$, found 337.2175, $C_{17}H_{34}NaO_3Si$ requires 337.2170.

*4.3.9. (2S,4R,5S)-2-tert-Butyldimethylsilyloxy-5-hydroxy-4-vinyl-3-heptanone (**15f**).* Colourless oil. R_f (95:5 hexanes/EtOAc) 0.20; $[\alpha]_D^{20}$ +143.8 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film) 3529 (br), 2958, 2932, 2859, 1712, 1635, 1473, 1255, 1118 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.84 (1H, ddd, *J* 17.0, 10.3, 9.1 Hz, C*H*=CH_2), 5.35–5.25 (1H, m, CH=CH_2), 4.25 (1H, q, *J* 6.9 Hz, C*H*OSi), 3.85–3.75 (2H, m, COC*H*C*H*OH), 1.60–1.27

(2H, m, C*H*$_2$Me), 1.32 (3H, d, *J* 6.9 Hz, *Me*CHOSi), 0.94 (3H, t, *J* 7.5 Hz, CH$_2$*Me*), 0.92 (9H, s, SiC*Me*$_3$), 0.08 (3H, s, Si*Me*), 0.07 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 214.9, 131.9, 121.1, 74.7, 72.5, 54.8, 27.1, 25.7, 21.6, 18.1, 10.1, −4.8, −4.9; HRMS (ESI): $[MNa]^+$, found 309.1861, $C_{15}H_{30}Na_3Si$ requires 309.1856.

*4.3.10. (2S,4R,5S)-2-tert-Butyldimethylsilyloxy-5-hydroxy-4,6-dimethyl-1-phenyl-3-heptanone (**19a**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.35; $[\alpha]_D^{20}$ +7.0 (*c* 1.2, $CHCl_3$); ν_{max} (liquid film) 3530 (br), 3087, 3064, 3031, 2960, 2711, 1697, 1604, 1496, 1474, 1407, 1389, 1362, 1324, 1257, 1195, 1109, 1039 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.32–7.16 (5H, m, Ar*H*), 4.26 (1H, dd, *J* 8.5, 4.0 Hz, C*H*OSi), 3.41 (1H, dd, *J* 9.1, 1.9 Hz, C*H*OH), 3.20 (1H, qd, *J* 7.3, 1.9 Hz, COC*H*Me), 3.01 (1H, dd, *J* 13.4, 4.0 Hz, PhCH_xH_y), 2.85 (1H, dd, *J* 13.4, 8.5 Hz, PhCH_xH_y), 1.74–1.60 (1H, m, C*H*Me$_2$), 1.05 (3H, d, *J* 7.3 Hz, COCH*Me*), 1.02 (3H, d, *J* 6.6 Hz, CH*Me*), 0.86 (9H, s, SiC*Me*$_3$), 0.86 (3H, d, *J* 6.8 Hz, CH*Me*), −0.08 (3H, s, Si*Me*), −0.36 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 219.2, 137.2, 130.0, 128.3, 126.8, 79.9, 75.9, 41.9, 41.8, 30.3, 25.7, 19.6, 18.7, 18.0, 8.7, −5.1, −5.7; HRMS (ESI): $[MH]^+$, found 365.2504, $C_{21}H_{37}O_3Si$ requires 365.2506.

*4.3.11. (1R,2R,4S)-4-tert-Butyldimethylsilyloxy-1-hydroxy-2-methyl-1,5-diphenyl-3-pentanone (**19c**).* Colourless oil. R_f (50:50 hexanes/CH_2Cl_2) 0.25; $[\alpha]_D^{20}$ +8.7 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3502 (br), 3063, 3030, 2954, 2929, 2885, 2857, 1699, 1454, 1255, 1115 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36–7.15 (10H, m, Ar*H*), 5.05 (1H, d, *J* 3.2 Hz, C*H*OH), 4.28 (1H, dd, *J* 8.5, 4.0 Hz, C*H*OSi), 3.24 (1H, qd, *J* 7.3, 3.2 Hz, COC*H*Me), 2.95 (1H, dd, *J* 13.5, 4.0 Hz, PhCH_xH_y), 2.77 (1H, dd, *J* 13.5, 8.5 Hz, PhCH_xH_y), 0.98 (3H, d, *J* 7.3 Hz, CH*Me*), 0.84 (9H, s, SiC*Me*$_3$), −0.06 (3H, s, Si*Me*), −0.32 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 218.0, 141.6, 137.2, 129.9, 128.3, 128.2, 127.2, 126.8, 125.9, 79.7, 72.4, 47.6, 41.4, 25.7, 18.0, 9.8, −5.1, −5.6; HRMS (ESI): $[MNa]^+$, found 421.2169, $C_{24}H_{34}NaO_3Si$ requires 421.2169.

*4.3.12. (3S,5R,6S)-3-tert-Butyldimethylsilyloxy-6-hydroxy-2,5,7-trimethyl-4-octanone (**20a**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.30; $[\alpha]_D^{20}$ −1.9 (*c* 1.3, $CHCl_3$); ν_{max} (liquid film) 3524 (br), 29.59, 2858, 1699, 1472, 1253, 1071 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.91 (1H, d, *J* 5.1 Hz, C*H*OSi), 3.40 (1H, dt, *J* 8.3, 1.6 Hz, C*H*OH), 3.14 (1H, qd, *J* 7.2, 1.6 Hz, COC*H*Me), 2.10–1.90 (1H, m, Me$_2$C*H*CHOSi), 1.80–1.60 (1H, m, HOCHC*H*Me$_2$), 1.09 (3H, d, *J* 7.2 Hz, COCH*Me*), 1.03 (3H, d, *J* 6.5 Hz, CH*Me*), 0.96 (3H, d, *J* 6.5 Hz, CH*Me*), 0.94 (9H, s, SiC*Me*$_3$), 0.89 (3H, d, *J* 6.7 Hz, CH*Me*), 0.84 (3H, d, *J* 6.7 Hz, CH*Me*), 0.05 (3H, s, Si*Me*), 0.03 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 218.9, 83.0, 76.0, 41.3, 32.1, 30.4, 25.8, 19.7, 19.4, 18.8, 18.2, 17.4, 9.3, −4.5, −5.1; HRMS (ESI): $[MNa]^+$, found 339.2328, $C_{17}H_{36}NaO_3Si$ requires 339.2325.

*4.3.13. (1R,2R,4S)-4-tert-Butyldimethylsilyloxy-1-hydroxy-2,5-dimethyl-1-phenyl-3-hexanone (**20c**).* Colourless oil. R_f (CH_2Cl_2) 0.25; $[\alpha]_D^{20}$ −20.5 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film) 3502 (br), 2958, 2930, 2857, 1717, 1456, 1252, 1071, 1004 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35–7.23 (5H, m, Ar*H*), 5.06 (1H, d, *J* 2.9 Hz, C*H*OH), 3.96 (1H, d, *J* 4.9 Hz, C*H*OSi), 3.18 (1H, qd, *J* 7.2, 2.9 Hz, COC*H*Me), 2.05–1.95 (1H, m, C*H*Me$_2$), 1.01 (3H, d, *J* 7.2 Hz, COCH*Me*), 0.95 (3H, d, *J* 6.6 Hz, CH*Me*), 0.94 (9H, s, SiC*Me*$_3$), 0.79 (3H, d, *J* 6.6 Hz, CH*Me*), 0.06 (3H, s, Si*Me*), 0.05 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 217.9, 141.5, 128.2, 127.2, 125.9, 82.7, 72.5, 46.9, 31.9, 25.8, 19.6, 18.2, 17.0, 10.3, −4.5, −5.1; HRMS (ESI): $[MNa]^+$, found 373.2169, $C_{20}H_{34}NaO_3Si$ requires 373.2169.

*4.3.14. (2S,4R,5S)-5-Hydroxy-4,6-dimethyl-2-triethylsilyloxy-3-heptanone (**24a**).* Colourless oil. R_f (CH_2Cl_2) 0.20; $[\alpha]_D^{20}$ +18.8 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3529 (br), 2960, 1702, 1459, 1368, 1121, 1105 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.24 (1H, q, *J* 6.9 Hz, C*H*OSi), 3.45 (1H, dd, *J* 8.5, 2.6 Hz, C*H*OH), 3.36 (1H, qd, *J* 7.2, 2.6 Hz, COC*H*Me), 1.69 (1H, dhept, *J* 8.6, 6.6 Hz, C*H*Me$_2$), 1.35 (3H, d, *J* 6.9 Hz, *Me*CHOSi), 1.12 (3H, d, *J* 7.2 Hz, COCH*Me*), 1.02 (3H, d, *J* 6.6 Hz, CH*Me*), 0.97 (9H, t, *J* 7.9 Hz, Si(CH$_2$*Me*)$_3$), 0.86 (3H, d, *J* 6.6 Hz, CH*Me*), 0.63 (6H, q, *J* 7.9 Hz, Si(C*H*$_2$Me)$_3$); δ_C (75.4 MHz, $CDCl_3$) 219.4, 76.1, 74.3, 41.3, 30.4, 21.4, 19.3, 18.8, 9.4, 6.7, 4.8; HRMS (ESI): $[MNa]^+$, found 311.2013, $C_{15}H_{32}NaO_3Si$ requires 311.2012.

*4.3.15. (2S,4R,5S)-2-tert-Butyldiphenylsilyloxy-5-hydroxy-4,6-dimethyl-3-heptanone (**25a**).* Colourless oil. R_f (CH_2Cl_2) 0.20; $[\alpha]_D^{20}$ +5.1 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3525 (br), 2962, 1700, 1474, 1428, 1113 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.66–7.60 (4H, m, Ar*H*), 7.48–7.33 (6H, m, Ar*H*), 4.27 (1H, q, *J* 7.0 Hz, C*H*OSi), 3.33–3.25 (1H, m, C*H*OH), 3.22 (1H, qd, *J* 7.0, 2.1 Hz, COC*H*Me), 1.70–1.54 (1H, m, C*H*Me$_2$), 1.28 (3H, d, *J* 7.0 Hz, *Me*CHOSi), 1.11 (9H, s, SiC*Me*$_3$), 1.03 (3H, d, *J* 7.0 Hz, COCH*Me*), 0.97 (3H, d, *J* 6.7 Hz, CH*Me*), 0.75 (3H, d, *J* 6.7 Hz, CH*Me*); δ_C (75.4 MHz, $CDCl_3$) 219.2, 135.8, 133.4, 132.7, 130.0, 127.8, 127.7, 75.9, 75.1, 41.7, 30.2, 26.9, 21.4, 19.5, 19.2, 18.7, 9.2; HRMS (FAB): $[MH]^+$, found 413.2507, $C_{25}H_{37}O_3Si$ requires 413.2511.

*4.3.16. (2S,4R,5S)-5-Hydroxy-4,6-dimethyl-2-triisopropylsilyloxy-3-heptanone (**26a**).* Colourless oil. R_f (CH_2Cl_2) 0.25; $[\alpha]_D^{20}$ +30.1 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film) 3529 (br), 2946, 1700, 1465, 1119 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.35 (1H, q, *J* 6.9 Hz, C*H*OSi), 3.49–3.43 (1H, m, C*H*OH), 3.40 (1H, qd, *J* 7.2, 2.1 Hz, COC*H*Me), 1.78–1.60 (1H, m, C*H*Me$_2$), 1.40 (3H, d, *J* 6.9 Hz, *Me*CHOSi), 1.16 (3H, d, *J* 7.2 Hz, COCH*Me*), 1.10–1.05 (21H, m, Si(C*H*Me$_2$)$_3$), 1.03 (3H, d, *J* 6.4 Hz, CH*Me*), 0.83 (3H, d, *J* 6.7 Hz, CH*Me*); δ_C (75.4 MHz, $CDCl_3$) 220.7, 76.0, 75.1, 41.1, 30.2, 22.2, 19.6, 18.7, 18.0, 17.9, 12.2, 9.3; HRMS (ESI): $[MH]^+$, found 331.2665, $C_{18}H_{39}O_3Si$ requires 331.2663.

4.4. Synthetic applications

*4.4.1. (2S,4R,5S,6S)-6-tert-Butyldiphenylsilyloxy-4-hexyl-2,5-dihydroxy-3-heptanone (**28**).* A solution of **12d** (695 mg, 1.16 mmol) and 48% aq HF (0.13 mL, 3.83 mmol) in CH_3CN (12 mL) was stirred at room temperature under a N_2 for 1 h. It was diluted with CH_2Cl_2 (100 mL), washed with sat $NaHCO_3$ (2×30 mL), dried (Na_2SO_4) and concentrated. Purification of the residue by column chromatography (80:20 hexanes/EtOAc) afforded 515 mg (1.06 mmol, 92% yield) of **28** as a colourless oil. R_f (80:20 hexanes/EtOAc) 0.35; $[\alpha]_D^{20}$ +11.1 (*c* 1.7, $CHCl_3$); ν_{max} (liquid film) 3450 (br), 3060, 2960, 2920, 2860, 1700, 1590, 1460 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.70–7.60 (4H, m, *ArH*), 7.50–7.30 (6H, m, Ar*H*), 4.23 (1H, qd, *J* 7.2, 4.8 Hz, MeC*H*OH), 3.83–3.72 (2H, m, C*H*OHC*H*OTBDPS), 3.18–3.12 (1H, m, COC*H*CH$_2$), 1.73–1.57 (1H, m, COCHCH_xH_y), 1.50–1.37 (1H, m, COCHCH_xH_y), 1.34 (3H, d, *J* 7.2 Hz, *Me*CHOH), 1.32–1.10 (8H, m, (C*H*$_2$)$_4$Me), 1.07 (9H, s, SiC*Me*$_3$), 1.04 (3H, d, *J* 5.8 Hz, TBDPSOCH*Me*), 0.87 (3H, t, *J* 6.9 Hz, CH$_2$*Me*), 0.08 (3H, s, Si*Me*), 0.08 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 217.0, 135.9, 135.8, 134.0, 133.1, 129.9, 129.7, 127.8, 127.5, 74.1, 73.4, 69.8, 47.4, 31.5, 29.6, 27.1, 27.0, 22.6, 20.6, 19.6, 19.2, 18.8, 14.0.

*4.4.2. (2R,3R,4S)-2-Hexyl-3-hydroxy-4-methylbutyrolactone, NFX-2 (**13**).* A solution of **28** (460 mg, 0.95 mmol) and $NaIO_4$ (2 g, 9.5 mmol) in 2:1 MeOH/H_2O (12 mL) was stirred at room temperature for 1.5 h. It was diluted with CH_2Cl_2 and washed with 0.5 M HCl. The aqueous layers were extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated to afford 424 mg of an oil that was used in the next step without further purification.

A solution of this oil and 48% aq HF (0.25 mL, 7.3 mmol) in CH_3CN (15 mL) was stirred at room temperature under N_2 for three days. Application of the work-up described in Section 4.4.1 afforded furnished 115 mg (0.57 mmol, 60% yield) of **13** as a white solid. R_f (2:1 hexanes/EtOAc) 0.30; mp 58.0–59.5 °C [lit.[34] mp 57.0–58.5 °C; lit.[35] mp 60–62 °C]. R_f (80:20 hexanes/EtOAc) 0.35; $[\alpha]_D^{20}$ −13.5 (*c* 1.2, MeOH) [lit.[34] $[\alpha]_D^{20}$ −11.9 (*c* 1.0, MeOH); lit.[35] $[\alpha]_D^{21}$ −14 (*c* 1.0, MeOH)]; ν_{max} (KBr) 3473 (br), 2952, 2930, 2850, 1735, 1395, 1210, 1187, 1063 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.20 (1H, quint, *J* 6.4 Hz, MeC*H*O), 3.89–3.79 (1H, m, C*H*OH), 2.56 (1H, ddd, *J* 8.5, 7.2, 5.7 Hz,

COC*H*CH_2), 1.90–1.20 (10H, m, (CH_2)$_5$Me), 1.45 (3H, d, *J* 6.4 Hz, *Me*CHO), 0.89 (3H, t, *J* 6.7 Hz, CH_2*Me*); δ_C (75.4 MHz, $CDCl_3$) 176.4, 80.1, 79.0, 48.6, 31.5, 29.2, 28.5, 26.7, 22.5, 18.2, 14.0.

*4.4.3. (2S,3R,4R,6S)-6-tert-Butyldimethylsilyloxy-2-tert-butyldiphenylsilyloxy-4-hexyl-5-oxo-3-heptanyl 3-methylbutanoate (**29**).* A solution of **12d** (843 mg, 1.4 mmol), pyridine (0.57 mL, 7.0 mmol), 3-methylbutanoyl chloride (0.84 mL, 7.0 mmol) and DMAP (25 mg) were stirred overnight at room temperature under N_2. It was diluted with CH_2Cl_2, washed with 1 M HCl, sat $NaHCO_3$ and H_2O, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (95:5 hexanes/EtOAc) to afford 907 mg (1.33 mmol, 94% yield) of **29** as a colourless oil. R_f (95:5 hexanes/EtOAc) 0.50; $[\alpha]_D^{20}$ −18.4 (*c* 1.6, $CHCl_3$); ν_{max} (liquid film) 3081, 3035, 2961, 2933, 2850, 1740, 1700, 1472, 1364, 1254, 1113 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.70–7.60 (4H, m, Ar*H*), 7.50–7.30 (6H, m, Ar*H*), 5.31 (1H, dd, *J* 6.9, 4.2 Hz, C*H*OCO), 4.18 (1H, q, *J* 6.7 Hz, C*H*OTBS), 3.70 (1H, dq, *J* 6.9, 6.3 Hz, C*H*OTBDPS), 3.66 (1H, ddd, *J* 10.4, 4.2, 3.0 Hz, COC*H*CH_2), 2.15–1.95 (3H, m, COCH_2C*H*Me_2), 1.67–1.57 (1H, m, COCHCH_xH$_y$), 1.30–1.20 (1H, m, COCHCH_xH$_y$), 1.20–1.10 (7H, m, CH_xH$_y$(CH_2)$_3$Me), 1.23 (3H, d, *J* 6.7 Hz, *Me*CHOTBS), 1.04 (9H, s, SiC*Me*$_3$), 0.95 (3H, d, *J* 6.3 Hz, *Me*CHOTBDPS), 0.95 (9H, s, SiC*Me*$_3$), 0.90–0.88 (1H, m, CH_xH$_y$(CH_2)$_3$Me), 0.89 (3H, d, *J* 6.3 Hz, CH*Me*), 0.88 (3H, d, *J* 6.3 Hz, CH*Me*), 0.85 (3H, t, *J* 7.0 Hz, CH_2*Me*), 0.15 (3H, s, Si*Me*), 0.12 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 213.0, 172.1, 136.0 (×2), 134.0, 133.0, 129.8, 129.6, 127.6, 127.4, 75.2, 74.9, 68.9, 45.7, 43.5, 31.7, 29.7, 27.4, 27.1, 26.0, 25.4, 25.0, 22.6, 22.4, 20.8, 20.2, 19.2, 18.1, 14.1, −4.5 (×2).

*4.4.4. (2R,3R,4S)-2-Hexyl-4-methyl-3-[3-methylbutanoyloxy]butyrolactone, antimycinone (**14**).* A solution of **29** (200 mg, 0.29 mmol), AcOH (33 μL, 0.58 mmol), 1 M TBAF in THF (1.75 mL, 1.75 mmol) in THF (5 mL) was stirred under N_2 for 1 h at 0 °C and 2 h at room temperature. It was diluted with Et_2O, washed with 10% $NaHSO_4$, sat $NaHCO_3$ and H_2O, dried ($MgSO_4$). Purification of the resulting oil by column chromatography (85:15 hexanes/EtOAc) furnished 88 mg (0.27 mmol, 91% yield) of a 4:1 mixture (^{1}H NMR analysis) of hemiketals **30** as a white solid.

A mixture of this solid and $NaIO_4$ (560 mg, 2.7 mmol) in 2:1 MeOH/H_2O (3.4 mL) was stirred at room temperature for 4 h. It was diluted with CH_2Cl_2, washed with 0.5 M HCl, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (80:20 hexanes/EtOAc) to afford 75 mg (0.27 mmol, 100% yield) of antimycinone **14** as a colourless oil. R_f (80:20 hexanes/EtOAc) 0.55; $[\alpha]_D^{20}$ +13.1 (*c* 1.5, $CHCl_3$) [lit.[36] $[\alpha]_D^{20}$ +10.6 (*c* 1.0, $CHCl_3$); lit.[20] $[\alpha]_D^{21}$ +10.1 (*c* 1.5, $CHCl_3$)];; ν_{max} (liquid film) 2959, 2930, 2873, 1785, 1744, 1468, 1294, 1252, 1181, 1121 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 4.94 (1H, dd, *J* 5.6, 4.6 Hz, C*H*OCO), 4.36 (1H, qd, *J* 6.6, 4.6 Hz, MeC*H*O), 2.68 (1H, dt, *J* 8.2, 5.6 Hz, COC*H*CH_2), 2.22 (2H, d, *J* 7.2 Hz, COCH_2), 2.18–2.03 (1H, m, C*H*Me_2), 1.92–1.79 (1H, m, COCHCH_xH$_y$), 1.73–1.56 (1H, m, COCHCH_xH$_y$), 1.50–1.20 (8H, m, (CH_2)$_4$Me), 1.47 (3H, d, *J* 6.6 Hz, *Me*CHO), 0.97 (6H, d, *J* 6.6 Hz, CHMe_2), 0.88 (3H, t, *J* 6.8 Hz, CH_2*Me*); δ_C (75.4 MHz, $CDCl_3$) 175.9, 172.4, 79.4, 78.4, 46.4, 43.1, 31.5, 29.3, 28.9, 26.8, 25.7, 22.5, 22.3, 19.4, 14.0.

*4.4.5. (3R,4S)-5-tert-Butyldimethylsilyloxy-4,6-dimethyl-3-heptanone (**31**).* A mixture of **8a** (330 mg, 1.15 mmol), 2,6-lutidine (0.20 mL, 1.72 mmol) and TBSOTf (0.33 mL, 1.44 mmol) in CH_2Cl_2 (4 mL) was stirred for 15 min at 0 °C and overnight at room temperature under N_2. It was partitioned with Et_2O and sat NH_4Cl and the organic layer was washed with H_2O. The aqueous layers were extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (99:1 hexanes/EtOAc) to afford 414 mg (1.03 mmol, 90% yield) of the fully protected aldol adduct.

A 0.2 M SmI_2 in THF (3.5 mL, 0.7 mmol) was slowly added via canula to a solution of that adduct (81 mg, 0.20 mmol) in 2:1 THF/MeOH (3.6 mL) at 0 °C under N_2. The dark green mixture was stirred for 10 min at 0 °C and was quenched by addition of sat Na_2CO_3 (12 mL). It was then partitioned with Et_2O and sat Na_2CO_3 and the aqueous layer was further extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was purified by column chromatography (90:10 hexanes/EtOAc) to afford 50 mg (0.18 mmol, 91% yield, 82% yield over two steps) of **31** as a colourless oil. R_f (90:10 hexanes/EtOAc) 0.60; $[\alpha]_D^{20}$ −18.4 (*c* 0.9, $CHCl_3$); ν_{max} (liquid film) 2960, 2860, 1715, 1465, 1254, 1054 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.78 (1H, dd, *J* 6.0, 4.1 Hz, C*H*OSi), 2.69 (1H, qd, *J* 7.0, 6.0 Hz, COC*H*Me), 2.60–2.39 (2H, m, CH_2CO), 1.64 (1H, heptd, *J* 6.9, 4.1 Hz, C*H*Me_2), 1.08 (3H, d, *J* 7.0 Hz, COCH*Me*), 1.03 (3H, t, *J* 7.2 Hz, *Me*CH_2CO), 0.90 (9H, s, SiC*Me*$_3$), 0.90 (3H, d, *J* 6.9 Hz, CH*Me*), 0.84 (3H, d, *J* 6.9 Hz, CH*Me*), 0.06 (3H, s, Si*Me*), 0.02 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 214.2, 77.5, 49.9, 35.5, 32.8, 26.1, 19.9, 18.4, 17.5, 13.6, 7.7, −3.9, −4.1; HRMS (FAB): $[MH]^+$, found 273.2245, $C_{15}H_{33}O_2Si$ requires 273.2250.

*4.4.6. (2R,3R,4R,5S)-2-tert-Butyldimethylsilyloxy-4,6-dimethyl-6-hepten-3,5-diol (ent-**34h**).* Et_2BOMe (1 M) in THF (3.0 mL, 3.0 mmol) was added to a solution of *ent*-**8h** (505 mg, 1.75 mmol) in THF (12.5 mL) at −78 °C under N_2. This mixture was stirred at −78 °C for 20 min. Solid $NaBH_4$ (80 mg, 2.1 mmol) was then added and the reaction mixture was stirred for 3 h at −78 °C, quenched with AcOH (3.5 mL) and vigorously stirred at room temperature. It was partitioned with CH_2Cl_2 and H_2O, the aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with 1 M NaOH and dried (Na_2SO_4). The volatiles were removed in vacuo and the resulting oil was treated with 33% w/v H_2O_2 (7 mL) in 1 M NaOAc in 9:1 MeOH/H_2O (50 mL) for 1 h at room temperature. It was partitioned with CH_2Cl_2 and H_2O, the aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the resulting oil by column chromatography (90:10 hexanes/EtOAc) afforded 477 mg (1.65 mmol, 94% yield) of *ent*-**34h** as a colourless oil. R_f (95:5 hexanes/EtOAc) 0.15; $[\alpha]_D^{20}$ +7.2 (*c* 2.1, $CHCl_3$); ν_{max} (liquid film) 3448 (br), 2956, 2932, 1654 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 5.11–5.10 (1H, m, C=CH_xH$_y$), 4.96–4.92 (1H, m, C=CH_xH$_y$), 4.26–4.23 (1H, m, CH_2=CC*H*OH), 3.76 (1H, dq, *J* 7.7, 6.0 Hz, C*H*OSi), 3.50 (1H, dd, *J* 7.7, 2.3 Hz, SiOCHC*H*OH), 1.78–1.22 (1H, m, C*H*Me), 1.70–1.68 (3H, m, *Me*C=CH_2), 1.13 (3H, d, *J* 6.0 Hz, *Me*CHOSi), 0.91 (9H, s, SiC*Me*$_3$), 0.83 (3H, d, *J* 7.0 Hz, CH*Me*), 0.11 (3H, s, Si*Me*), 0.10 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 144.7, 111.1, 80.4, 78.8, 70.3, 35.7, 25.8, 19.8, 19.5, 18.0, 5.3, −4.0, −4.8; HRMS (FAB): $[MH]^+$, found 290.2226, $C_{15}H_{33}O_3Si$ requires 290.2232.

*4.4.7. (2S,3R,4S,5R,6R)-6-tert-Butyldimethylsilyloxy-2,4-dimethyl-1,3,5-heptanetriol (**35**).* BH_3·THF (1 M) in THF (1.6 mL, 1.6 mmol) was carefully added to a solution of *ent*-**34h** (150 mg, 0.52 mmol) in THF (5 mL) at 0 °C under N_2. The resulting solution was stirred at room temperature for 2 h, cooled at 0 °C, diluted with 1:1 THF/MeOH (5.8 mL), and treated with 33% w/v H_2O_2 (1.6 mL) and 3 M NaOH (4.8 mL). The reaction mixture was then stirred for 2 h at room temperature. It was partitioned with EtOAc and H_2O, the aqueous layer was extracted with EtOAc and the combined organic extracts were dried ($MgSO_4$) and concentrated. Purification of the resulting oil by column chromatography (from CH_2Cl_2 to 95:5 CH_2Cl_2/*i*-PrOH) afforded 153 mg (96% yield) of a 4:1 mixture of two diastereomers according to its ^{1}H NMR analysis. Further purification by MPLC (95:5 CH_2Cl_2/*i*-PrOH) provided 96 mg (0.31 mmol, 60% yield) of diastereomerically pure triol **35** as a colourless oil. R_f (95:5 CH_2Cl_2/*i*-PrOH) 0.75; $[\alpha]_D^{20}$ −14.5 (*c* 2.0, $CHCl_3$); ν_{max} (liquid film) 3394 (br), 2956, 2933, 1381 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.81 (1H, dd, *J* 5.4, 4.4 Hz, C*H*OHCHCH_2OH), 3.75 (1H, dq, *J* 8.1, 6.3 Hz, C*H*OSi), 3.66 (2H, d, *J* 4.8 Hz, CH_2OH), 3.41 (1H, dd, *J* 8.2, 2.2 Hz, SiOCHC*H*OH), 2.00–1.90 (1H, m, C*H*Me), 1.77–1.72 (1H, m,

C*H*CH_2OH), 1.11 (3H, d, *J* 6.3 Hz, *Me*CHOSi), 1.03 (3H, d, *J* 7.0 Hz, CH*Me*), 0.96 (3H, d, *J* 7.0 Hz, CH*Me*), 0.90 (9H, s, SiC*Me*$_3$), 0.11 (6H, s, 2× Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 79.2, 77.2, 70.4, 66.7, 37.2, 36.0, 25.8, 19.6, 17.9, 11.5, 7.2, −4.1, −4.8; HRMS (FAB): $[MH]^+$, found 307.2318, $C_{15}H_{35}O_4Si$ requires 307.2304.

*4.4.8. (2S,3R,4S,5R,6R)-6-tert-Butyldimethylsilyloxy-3,5-isopropylidenoxy-2,4-dimethyl-1-heptyl pivalate (**36**).* Freshly distilled pivaloyl chloride (0.28 mL, 2.3 mmol) was added to a solution of **35** (154 mg, 0.46 mmol), Et_3N (0.32 mL, 2.3 mmol) and DMAP (cat) in CH_2Cl_2 (4.5 mL) at 0 °C under N_2. The reaction mixture was stirred for 1 h at 0 °C and overnight at room temperature. It was diluted with CH_2Cl_2, washed with 1 M HCl, sat $NaHCO_3$ and H_2O, dried ($MgSO_4$) and concentrated. The residue was filtered through a pad of silica (99:1 CH_2Cl_2/MeOH) to afford a colourless oil, which was used immediately in the next step.

A solution of this oil and PPTS (cat) in 1:1 CH_2Cl_2/$Me_2C(OMe)_2$ (5 mL) was stirred overnight at room temperature under N_2. Removal of the volatiles and purification of the residue by column chromatography (CH_2Cl_2) gave 121 mg (0.28 mmol, 61% yield) of **36** as a colourless oil. R_f (CH_2Cl_2) 0.70; $[\alpha]_D^{20}$ +9.5 (*c* 1.25, $CHCl_3$); ν_{max} (liquid film) 2965, 2933, 1732 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.00 (1H, dd, *J* 11.1, 4.1 Hz, CH_xH_yOPiv), 3.89 (1H, dd, *J* 11.1, 5.7 Hz, CH_xH_yOPiv), 3.71 (1H, dq, *J* 8.2, 6.2 Hz, C*H*OSi), 3.56 (1H, dd, *J* 9.7, 2.0 Hz, C*H*OCHCH_2O), 3.49 (1H, dd, *J* 8.2, 2.0 Hz, SiOCHC*H*OH), 1.98–1.90 (1H, m, C*H*CH_2O), 1.45 (1H, qt, *J* 6.7, 2.0 Hz, C*H*Me), 1.39 (3H, s, O_2C*Me*), 1.38 (3H, s, O_2C*Me*), 1.19 (9H, s, C*Me*$_3$), 1.05 (3H, d, *J* 6.2 Hz, *Me*CHOSi), 1.02 (3H, d, *J* 6.6 Hz, *Me*CHCH_2), 0.87 (9H, s, SiC*Me*$_3$), 0.85 (3H, d, *J* 6.7 Hz, CH*Me*), 0.06 (3H, s, Si*Me*), 0.04 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 178.5, 99.0, 78.9, 75.6, 69.2, 65.6, 38.9, 33.9, 31.1, 29.8, 27.2, 25.8, 19.3, 18.8, 18.3, 14.5, 5.4, −4.3, −5.0; HRMS (FAB): $[MH]^+$, found 431.3191, $C_{23}H_{47}O_5Si$ requires 431.3192.

*4.4.9. (2S,3R,4S,5R)-3,5-Isopropylidenoxy-2,4-dimethyl-6-oxo-1-heptyl pivalate (**37**).* TBAF (2 M) in THF (0.6 mL, 1.2 mmol) was added to a solution of **36** (49 mg, 0.11 mmol) in THF (1.5 mL) at 0 °C under N_2 and the reaction mixture was stirred at room temperature for 20 min. It was diluted with CH_2Cl_2, washed with H_2O and brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (75:25 hexanes/EtOAc) to afford 29 mg of an oil. A solution of this oil in CH_2Cl_2 (1 mL) was added via canula (+ 0.8 mL CH_2Cl_2) to a solution of DMP (90 mg, 0.21 mmol) and pyridine (41 μL, 0.51 mmol) in CH_2Cl_2 (1 mL) at 0 °C under N_2, and the reaction mixture was stirred overnight at room temperature. The resulting white suspension was diluted with EtOAc, washed with H_2O, sat $NaHCO_3$ and $Na_2S_2O_3$ and dried ($MgSO_4$). Removal of the volatiles afforded a residue that was purified by column chromatography (90:10 hexanes/EtOAc) to give 25 mg (79 μmol, 70% yield) of keto ester **37** as a colourless oil. R_f (90:10 hexanes/EtOAc) 0.15; $[\alpha]_D^{20}$ +27.5 (*c* 1.2, $CHCl_3$); ν_{max} (liquid film) 2975, 2933, 1728 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.25 (1H, d, *J* 2.4 Hz, MeCOC*H*O), 4.06 (1H, dd, *J* 11.1, 4.5 Hz, CH_xH_yOPiv), 3.85 (1H, dd, *J* 11.1, 6.0 Hz, CH_xH_yOPiv), 3.66 (1H, dd, *J* 9.9, 2.1 Hz, C*H*OCHCH_2O), 2.18 (3H, s, *Me*CO), 2.06–2.00 (1H, m, C*H*Me), 2.00–1.92 (1H, m, C*H*CH_2O), 1.49 (3H, s, O_2C*Me*), 1.42 (3H, s, O_2C*Me*), 1.21 (9H, s, C*Me*$_3$), 1.01 (3H, d, *J* 6.6 Hz, CH*Me*), 0.86 (3H, d, *J* 6.9 Hz, CH*Me*); δ_C (75.4 MHz, $CDCl_3$) 209.5, 178.4, 99.5, 79.3, 75.1, 65.4, 38.9, 34.1, 32.5, 29.8, 27.2, 27.1, 19.0, 14.2, 6.4; HRMS (FAB): $[MH]^+$, found 315.2174, $C_{17}H_{31}O_5$ requires 315.2171.

4.5. Sequential aldol and reduction transformation from allyl ketone 5

Neat $TiCl_4$ (0.12 mL, 1.1 mmol) was added slowly to a solution of **5** (228 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at −78 °C under N_2. The resulting yellow suspension was stirred for 3–4 min and *i*-Pr_2NEt (0.19 mL, 1.1 mmol) was added dropwise. The resulting dark red solution was stirred for 30 min at −78 °C, freshly distilled aldehyde was added and stirring continued for 30 min at −78 °C. Then, 2 M $LiBH_4$ in THF (1.0 mL, 2.0 mmol) was added carefully and the reaction mixture was stirred for 1 h at −78 °C. Finally, the reaction was quenched by slow addition of AcOH (1 mL), followed by sat NH_4Cl (5 mL). The mixture was partitioned with Et_2O and H_2O, and the organic layer was washed with sat $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (90:10 hexanes/EtOAc) to give the corresponding diol.

*4.5.1. (2S,3S,4R,5S)-2-tert-Butyldimethylsilyloxy-6-methyl-4-vinyl-3,5-heptanediol (**38a**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.25; $[\alpha]_D^{20}$ +18.7 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film) 3527 (br), 3073, 2956, 2931, 2858, 1637, 1472, 1463, 1387, 1255, 1133, 1073 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.01 (1H, dt, *J* 17.4, 10.4 Hz, C*H*=CH_2), 5.25 (1H, dd, *J* 10.4, 2.2 Hz, CH=CH_xH_y), 5.05 (1H, dd, *J* 17.4, 2.2 Hz, CH=CH_xH_y), 3.68 (1H, dq, *J* 8.1, 6.0 Hz, C*H*OSi), 3.55–3.40 (2H, m, 2× C*H*OH), 2.30–2.20 (1H, m, C*H*CH=CH_2), 1.85–1.65 (1H, m, C*H*Me_2), 1.10 (3H, d, *J* 6.0 Hz, *Me*CHOSi), 0.98 (3H, d, *J* 6.6 Hz, CH*Me*), 0.90 (9H, s, SiC*Me*$_3$), 0.88 (3H, d, *J* 6.9 Hz, CH*Me*), 0.09 (3H, s, Si*Me*), 0.08 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 133.3, 118.8, 80.0, 79.6, 70.5, 47.2, 30.6, 25.8, 19.3, 19.2, 18.4, 18.0, −4.1, −4.8; HRMS (ESI): $[MH]^+$, found 303.2352, $C_{16}H_{35}O_3Si$ requires 303.2350.

*4.5.2. (1R,2R,3S,4S)-4-tert-Butyldimethylsilyloxy-1-phenyl-2-vinyl-1,3-pentanediol (**38c**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.20; $[\alpha]_D^{20}$ +30.3 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3737, 3688 (br), 3072, 2955, 2929, 2857, 1636, 1472, 1256, 1085 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40–7.20 (5H, m, Ar*H*), 6.05 (1H, dt, *J* 17.4, 10.2 Hz, C*H*=CH_2), 5.23 (1H, dd, *J* 10.2, 2.1 Hz, CH=CH_xH_y), 4.95 (1H, d, *J* 5.9 Hz, C*H*OHPh), 4.91 (1H, ddd, *J* 17.4, 2.1, 0.5 Hz, CH=CH_xH_y), 3.63 (1H, dq, *J* 8.3, 6.0 Hz, C*H*OSi), 3.32 (1H, dd, *J* 8.2, 2.3 Hz, CHOSiC*H*OH), 2.30–2.23 (1H, m, C*H*CH=CH_2), 1.00 (3H, d, *J* 6.0 Hz, *Me*CHOSi), 0.89 (9H, s, SiC*Me*$_3$), 0.08 (3H, s, Si*Me*), 0.06 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 142.2, 132.9, 128.0, 127.3, 126.7, 120.1, 77.7, 75.9, 70.7, 53.6, 25.8, 19.0, 18.0, −4.1, −4.8; HRMS (ESI): $[MNa]^+$, found 359.2011, $C_{19}H_{32}NaO_3Si$ requires 359.2012.

*4.5.3. (2S,3S,4R,5S)-2-tert-Butyldimethylsilyloxy-7-methyl-4-vinyl-3,5-octanediol (**38e**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.25; $[\alpha]_D^{20}$ −0.5 (*c* 1.1, $CHCl_3$); ν_{max} (liquid film) 3534 (br), 3073, 2955, 2930, 2859, 1637, 1471, 1256, 1134, 1084 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.00 (1H, dt, *J* 17.4, 10.2 Hz, C*H*=CH_2), 5.26 (1H, dd, *J* 10.2, 2.3 Hz, CH=CH_xH_y), 5.03 (1H, dd, *J* 17.4, 2.3 Hz, CH=CH_xH_y), 4.00–3.93 (1H, m, C*H*OHCH_2), 3.67 (1H, dq, *J* 8.2, 6.0 Hz, C*H*OSi), 3.58–3.52 (1H, m, CHOSiC*H*OH), 2.01–1.94 (1H, m, C*H*CH=CH_2), 1.86–1.70 (1H, m, C*H*Me_2), 1.45 (1H, ddd, *J* 13.8, 8.9, 5.4 Hz, CHOHCH_xH_y), 1.12–1.10 (1H, m, CHOHCH_xH_y), 1.09 (3H, d, *J* 6.0 Hz, *Me*CHOSi), 0.92 (3H, d, *J* 6.6 Hz, CH*Me*), 0.92 (3H, d, *J* 6.6 Hz, CH*Me*), 0.90 (9H, s, SiC*Me*$_3$), 0.09 (3H, s, Si*Me*), 0.09 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 133.0, 119.2, 79.7, 72.3, 70.5, 50.4, 43.8, 25.8, 24.3, 23.4, 22.1, 19.1, 18.0, −4.1, −4.8; HRMS (ESI): $[MH]^+$, found 317.2512, $C_{17}H_{37}O_3Si$ requires 317.2514.

*4.5.4. (2S,3S,4R,5S)-2-tert-Butyldimethylsilyloxy-4-vinyl-3,5-octadecanediol (**38i**).* Colourless oil. R_f (90:10 hexanes/EtOAc) 0.30; $[\alpha]_D^{20}$ +2.9 (*c* 1.0, $CHCl_3$); ν_{max} (liquid film) 3536 (br), 3073, 2926, 2855, 1636, 1463, 1255, 1087 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.00 (1H, dt, *J* 17.3, 10.3 Hz, C*H*=CH_2), 5.26 (1H, dd, *J* 10.3, 2.1 Hz, CH=CH_xH_y), 5.03 (1H, dd, *J* 17.4, 2.1 Hz, CH=CH_xH_y), 3.86–3.83 (1H, m, C*H*OHCH_2), 3.66 (1H, dq, *J* 8.0, 6.0 Hz, C*H*OSi), 3.54–3.49 (1H, m, CHOSiC*H*OH), 2.07–2.00 (1H, m, C*H*CH=CH_2), 1.25 (24H, br s, $(CH_2)_{12}$Me), 1.09 (3H, d, *J* 6.0 Hz, *Me*CHOSi), 0.90 (9H, s, SiC*Me*$_3$), 0.90–0.88 (3H, buried m, $(CH)_{12}$*Me*), 0.09 (3H, s, Si*Me*), 0.09 (3H, s, Si*Me*); δ_C (75.4 MHz, $CDCl_3$) 133.0, 119.2, 79.7, 74.6, 70.5, 49.9, 34.7,

31.9, 29.7–29.6 (×8), 29.3, 25.8, 22.7, 19.2, 18.0, 14.1, −4.1, −4.8; HRMS (ESI): $[MH]^+$, found 443.3916, $C_{26}H_{55}O_3Si$ requires 443.3915.

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